Select Health Medical Policies

Hematology/Oncology Policies

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MEDICAL POLICY

CHELATION THERAPY

Policy # 296

Implementation Date:2/15/06

Review Dates: 5/17/07, 4/24/08, 4/23/09, 2/18/10, 5/19/11, 6/21/12, 6/20/13, 4/17/14, 5/7/15, 4/14/16, 4/27/17, 7/16/18, 4/15/19, 4/12/20, 4/14/21, 3/2/22, 4/20/23, 4/17/24, 3/30/25

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Related Medical Policies:

#589 Complementary and Alternative Medicine

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Chelation therapy consists of the intravenous or oral administration of chelating agents, such as that remove metal ions, such as lead, zinc, iron, copper, and calcium from the body. Chelation therapy consists of the intravenous or oral administration of chelating agents, which are used to bind metals into stable compounds with relatively low toxicity and to enhance their excretion. The principal chelating agents include deferoxamine mesylate, dimercaprol (British Anti-Lewisite, BAL), edetate (EDTA), succimer (DMSA, dimercaptosuccinic acid), and penicillamine. The specific use of these chelating agents depends on the metal involved and the clinical status of the patient.

Chelation therapy is an established treatment for metal toxicity, particularly for patients who are symptomatic as a direct result of excessive body loads of iron, lead, arsenic, mercury, or copper.

Chelation therapy has not been shown to be effective for atherosclerosis, coronary artery disease, peripheral vascular disease, angina, or ischemic heart disease. The best scientific evidence suggests that the therapy is ineffective. Insufficient clinical evidence exists to support the use of chelation therapy in such diseases as arthritis, diabetes, hyperlipidemia, hypoglycemia, multiple sclerosis, peripheral vascular disease, porphyria, or scleroderma.

COMMERCIAL PLAN POLICY/CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers chelation therapy for the treatment of metal ion toxicity and specific other medical conditions as listed below. This therapy is established and found to be medically necessary in the treatment of these conditions.

Conditions for which chelation therapy is covered:

1. Heavy metal poisoning (iron, lead, cadmium, mercury, copper, arsenic, gold)
2. Cooley's anemia (thalassemia major)
3. Cystinuria
4. Wilson's disease
5. Sickle cell anemia
6. Primary or secondary hemochromatosis when phlebotomy is not an option
7. Aluminum toxicity in members undergoing dialysis

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8. Aceruloplasminemia (hereditary ceruloplasmin deficiency)
9. Biliary cirrhosis
10. Diamond-Blackfan anemia
11. Secondary hemochromatosis (i.e., due to iron overload from multiple transfusions including persons with IPSS Low- or Intermediate-1-risk myelodysplastic syndrome

Select Health does NOT cover chelation therapy for any other clinical situations, including but not limited to, the treatment of atherosclerotic disease, arthritis, hyperlipidemia, diabetes mellitus, autism, porphyria, scleroderma, or multiple sclerosis. This meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Chelating agents, also known as heavy metal antagonists, form complexes with toxic heavy metals, rendering them physiologically inactive and enhancing their excretion in the urine. Specific chelating agents include EDTA, deferoxamine (Desferal), dimercaprol (BAL in oil), and penicillamine (Cuprimine, Depen).

There is insufficient evidence to support the use of chelation therapy for prevention or treatment of cardiovascular disease. Villaruz et al.'s review of chelation therapy for cardiovascular disease reached the following conclusions:

> At present, there is insufficient evidence to decide on the effectiveness or ineffectiveness of chelation therapy in improving clinical outcomes of patients with atherosclerotic cardiovascular disease. This decision must be preceded by conducting randomized controlled trials that would include endpoints that show the effects of chelation therapy on longevity and quality of life among patients with atherosclerotic cardiovascular disease.

An assessment of chelation therapy by the West Midlands Health Technology Assessment Collaboration concluded that: "… currently there is little objective evidence that CT [chelation therapy] is effective for CHD [coronary heart disease] or IC [intermittent claudication]."

In August 2002, the National Center for Complementary and Alternative Medicine (NCCAM) and the National Heart, Lung, and Blood Institute (NHLBI) announced that they have launched the Trial to Assess Chelation Therapy (TACT), which is the first large-scale, multicenter study to find out if EDTA chelation therapy is safe and effective for people with coronary heart disease. This placebo-controlled, double-blind study will involve 2,372 participants age 50 years and older with a history of myocardial infarction. Recruitment for this study began in March 2003, and the study will take 5 years to complete.

In a randomized double-blind, placebo-controlled study (n = 47), Anderson et al. reported that EDTA chelation therapy in combination with vitamins and minerals did not provide additional benefits on

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abnormal vasomotor responses in patients with coronary artery disease optimally treated with proven therapies for atherosclerotic risk factors.

Recently, chelation therapy has also been advocated by some practitioners to treat patients with autism. However, there is a lack of scientific evidence regarding its effectiveness for this indication. Well-designed clinical trials are needed to ascertain the clinical value, if any, of chelation therapy for autistic individuals. The precise pathogenesis of keloid formation is unknown.

Billing/Coding Information

Covered: For the indications listed above only

CPT CODES

96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	; each additional hour (List separately in addition to code for primary procedure)
96367	; additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)

HCPCS CODES

J0470	Injection, dimercaprol, per 100 mg
J0600	Injection, edetate calcium disodium up to 1,000 mg
J0895	Injection, deferoxamine mesylate, 500 mg
J3520	Edetate disodium, per 150 mg
S9355	Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

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Revision History

Revision Date	Summary of Changes
4/29/24	For Commercial Plan Policy, modified criterion #6: "Primary or secondary hemochromatosis when phlebotomy is not an option" and added criterion #7: "Aluminum toxicity in members undergoing dialysis."
7/10/25	For Commercial Plan Policy, added the following four conditions as qualifying options to coverage criteria: "8. Aceruloplasminemia (hereditary ceruloplasmin deficiency); 9. Biliary cirrhosis; 10. Diamond-Blackfan anemia; 11. Secondary hemochromatosis (i.e., due to iron overload from multiple transfusions including persons with IPSS Low- or Intermediate-1-risk myelodysplastic syndrome."

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Chelation Therapy, continued

Disclaimer
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The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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MEDICAL POLICY

CRYOABLATION FOR RENAL CELL CARCINOMA (RCC)

Policy # 337
Implementation Date:3/22/07
Review Dates: 2/21/08, 2/26/09, 2/18/10, 2/17/11, 2/16/12, 2/20/14, 5/19/15, 4/22/16, 6/15/17, 9/18/18, 8/8/19, 8/20/20, 8/19/21, 7/27/22, 8/23/23, 8/21/24
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Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Renal cell carcinomas (RCCs), which originate within the renal cortex, are responsible for 80%–85% of all primary renal neoplasms. In 2006, 39,000 people will be diagnosed and almost 13,000 will die from RCC in the United States. Historically, the disease has been more common in men, though, this gap has narrowed in recent years. RCC occurs predominantly in the sixth to eighth decade of life; it is unusual in patients under 40 years of age and rare in children.

Surgery (radical or partial nephrectomy) is the standard of care for most non-metastatic RCC cases and is curative in most cases. However, less invasive options are available that attempt to preserve renal function in otherwise healthy kidneys, and which can be performed on an outpatient basis. One such therapy is cryoablation, a form of in-situ tumor ablation in which subfreezing temperatures are delivered by a cryoprobe to cool renal tissue to the point of irreversible destruction. The essential mechanism of cryoablation is direct thermal destruction of renal cells, followed by thromboembolic ischemia of the targeted tissue. The cryoprobe is cooled by liquid nitrogen or argon gas. Probes are available in a variety of models and diameters (1.5–8 mm) and are suitable for open, laparoscopic, and percutaneous use. Cryoablation for RCC may be conducted using open, laparoscopic, or percutaneous techniques.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers cryoablation for treatment of renal cell carcinoma in *limited clinical circumstances.*

Conditions for which coverage of cryoablation therapy in the treatment of renal cell carcinoma are allowed include (any one of the following criteria):

1. Patients, who in the opinion of their surgeon and primary care provider, could not tolerate a partial/total nephrectomy due to other underlying chronic medical conditions; or
2. Patients with reduced renal function identified by a glomerular filtration rate ≤ 60 ml/min, serum creatinine ≥ 2.0, with a BUN-to-creatinine ratio < 20/1; or
3. Patients who have an increased risk of complications associated with other therapies or who have other medical co-morbidities; or
4. Patient's renal mass is less than or equal to 3 cm.

Cryoablation for Renal Cell Carcinoma (RCC), continued

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Open cryoablation requires an incision large enough for kidney mobilization and tumor exposure. Multiple cryoprobes are placed at 1 cm intervals along the periphery, base, and center of the tumor in order to form a wedge-shaped lesion. Tip positioning is guided by ultrasound. Ultrasound is used to confirm normal blood flow to the surrounding kidney and obliteration of flow to the ablated lesion. The open approach maximizes mobilization and exposure of the kidney and facilitated ultrasound monitoring.

Laparoscopic cryoablation resembles the open approach, but uses instruments modified for laparoscopy, including an intraoperative, laparoscopic ultrasound probe, resulting in less morbidity. The procedure may be performed using a transperitoneal or retroperitoneal approach depending on the location of the lesion and surgeon preference. This procedure allows real-time monitoring of the ice ball through intraoperative ultrasound and direct vision, and permits mobilization of the kidney, reduced contact and injury to adjacent organs, and extensive pathologic sampling. Anterior or medial tumors can be safely approached laparoscopically.

In percutaneous cryoablation, sheaths are positioned in the kidney in the vicinity of renal lesions, typically under MRI guidance. Cryoprobes are then placed through these sheaths and cryoablation is initiated. MRI is of limited use in identifying actual kill zones. Percutaneous cryoablation is limited in that only posterior and lateral tumors can be readily accessed. Because adjacent organs cannot be moved, there is a greater risk of adjacent organ hypothermia and damage, which can result in severe morbidities.

The FDA has approved cryoablation systems from several manufacturers including SeedNet (Oncura, Plymouth Meeting, PA) and the Cryocare CN2 System (Endocare, Irvine, CA).

Song reviewed the long-term outcome of laparoscopic and percutaneous cryoablation for stage is T1ANT1B renal cell carcinoma. 163 consecutive patients were treated. Median size of the mass was 2.9 cm. Mean follow-up was 64 months ±30 months with a range of 7 to 127 months. Local recurrence was observed in 8% of patients. Progression free survival at 5 years was 95.5% and the laparoscopic group and 96.7% in the percutaneous group. The conclusions of the author was that cryotherapy whether that be laparoscopic or percutaneous for T1 renal cell carcinoma provides satisfactory oncological results and preserves renal function with acceptable complication rates.

Laso-Garcia evaluated the oncological results and safety of cryotherapy for T1ANT1B renal tumors. 67 patients were treated. Mean tumor size was 2.6 cm. The majority of patients were treated percutaneously rather than laparoscopic. 60 patients had biopsy-proven renal cell carcinoma prior to cryotherapy. Main follow-up was 52.7 months. Recurrence has occurred and 22.5% of cases. One quarter of these were treated with repeat cryotherapy. 31% were treated with radical nephrectomy. 43.8% were treated with active surveillance. The overall survival at 12, 24, and 48 months was 48.5%, 46.8%, and 76.9% respectively. There was no cancer-specific mortality with a mean follow-up of 52.7 months.

Select Health

Cryoablation for Renal Cell Carcinoma (RCC), continued

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

50250	Ablation, open, one or more renal mass lesion(s), cryosurgical, including intraoperative ultrasound, if performed
50542	Laparoscopy, surgical; ablation of renal mass lesion(s), including intraoperative ultrasound guidance and monitoring, when performed
50593	Ablation, renal tumor(s), unilateral, percutaneous, cryotherapy

HCPCS CODES

No specific codes identified

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Cryoablation for Renal Cell Carcinoma (RCC), continued

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Revision History

Revision Date	Summary of Changes
5/27/25	For Commercial Plan Policy, modified requirements in criterion #3: “Patients who have an increased risk of complications associated with other therapies or who have other medical co-morbidities.”

Select Health

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MEDICAL POLICY

CYTOREDUCTIVE SURGERY (CRS) WITH ASSOCIATED HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

Policy # 494

Implementation Date:12/5/11

Review Dates: 7/18/13, 8/28/14, 8/20/15, 3/24/16, 8/25/16, 8/17/17, 9/18/18, 8/8/19, 8/20/20, 8/19/21, 7/26/22, 8/16/23, 8/17/24

Revision Dates: 5/22/17, 9/26/17, 11/6/24, 5/9/25, 6/11/25

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

For some cancers with a significant peritoneal component, systemic chemotherapy has been historically largely ineffective due to poor penetration into the peritoneal cavity and limited activity of chemotherapeutic agents against the primary tumor. Studies with newer chemotherapeutic agents are lacking. Similarly, cytoreductive surgery (debulking surgery) is also of limited benefit in isolation in many peritoneal malignancies due to the presence of micrometastases which are not excised. Given the lack of efficacy for many standard therapies, alternative methods to treat primary or secondary peritoneal cancer have been investigated. Hyperthermic intraperitoneal chemotherapy (HIPEC) is one technique which has been investigated as an alternative in an attempt to overcome some of these limitations.

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is used as an adjunct to surgery for the treatment of some cancers which have metastasized within the peritoneal cavity. HIPEC is delivered into the peritoneal space once the cytoreductive surgical procedure is completed. The goal of HIPEC is to enhance the cytotoxic effect of chemotherapeutic drugs, thereby eliminating micrometastases and disseminated tumor cells remaining in the peritoneal space. The chemotherapeutic agents employed in HIPEC need to have a cell cycle nonspecific mechanism of action and should ideally show a heat synergistic cytotoxic effect. Specific technical training and a solid knowledge of regional chemotherapy management are required. Treatment-related toxicity is a risk and should be considered during patient selection process.

HIPEC is performed immediately following surgery performed to remove all visible evidence of an abdominal tumor. Once the tumor has been removed, the surgeon continuously circulates a heated, sterile chemotherapy solution throughout the peritoneal cavity for up to 90 minutes. The HIPEC procedure is designed to attempt to kill any remaining cancer cells once all visible disease is removed. The solution is then removed, and the incision is then closed. Several safeguards are instituted to protect the patient from the toxic effects of the heat and chemotherapy. Preoperatively, the patient is placed on a cooling blanket which is used during the HIPEC to keep the core temperature within a range of 97°–102°F. During the perfusion, the ambient temperature in the operating room is turned down to 60°F, while the patient's core temperature is monitored with an esophageal and bladder temperature probe.

HIPEC has been studied in several malignancies, including appendiceal cancer with pseudomyxoma peritonei malignant mesothelioma, metastatic colorectal cancer with peritoneal seedings, ovarian cancer, and others.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health

Cytoreductive Surgery (CRS) with Associated Hyperthermic Intraperitoneal Chemotherapy (HIPEC), continued

Select Health covers cytoreductive surgery (CRS) with associated hyperthermic intraperitoneal chemotherapy (HIPEC) in any of the following clinical circumstances:

1. For the treatment of patients with mucinous appendiceal carcinoma with pseudomyxoma peritonei or diffuse malignant peritoneal mesothelioma; or

2. For patients with stage III ovarian cancer; or

3. For patients diagnosed with metastatic colon cancer to the peritoneum, if the following are not present: biliary obstruction, extensive disease at the gastrohepatic ligament/porta hepatis, extensive retroperitoneal disease, intraparenchymal liver lesions (requiring major resection), diffuse small bowel serosa/mesenteric involvement, and/or multiple sites of small bowel obstruction; or

4. For patients diagnosed with gastric cancer, only with peritoneal carcinoma with a low PCI (≤ 10), and who are candidates to undergo complete cytoreduction; and who have completed at least 3 months of chemotherapy.

Select Health does NOT cover cytoreductive surgery (CRS) with associated hyperthermic intraperitoneal chemotherapy (HIPEC) for all other indications as it is considered experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Pseudomyxoma peritonei. In 2008, Elias et al. reported the results of 105 consecutive patients with pseudomyxoma peritonei treated between 1994 and 2006 with CRS and HIPEC. The primary tumor was the appendix in 93 patients, ovary in 3, urachus in 1, pancreas in 1, and indeterminate in 7. Tumor histology was disseminated peritoneal adenomucinosis in 48% of patients, intermediate in 35%, and peritoneal mucinous carcinomatosis in 17%. At the end of surgery, 72% of patients had no visible residual peritoneal lesions. Postoperative mortality was 7.6%, and morbidity 67.6%. Median follow-up was 48 months, and 5-year OS and DFS were 80% (95% confidence interval [CI], 68% to 88%) and 68% (95% CI, 55% to 79%), respectively. On multivariate analysis, two factors that had a negative influence on DFS were identified: serum carbohydrate antigen (CA) 19.9 level (a marker of biliopancreatic malignancy) greater than 300 units/mL and non-disseminated peritoneal adenomucinosis tumor histology.

A retrospective, multicenter cohort study (Glehen et al., 2010) to evaluate toxicity and prognostic factors after CRS and HIPEC and/or unheated intraperitoneal chemotherapy for 5 days postoperatively. Patients had diffuse peritoneal disease from malignancies of multiple different histologic origins. Exclusion criteria were perioperative chemotherapy performed more than 7 days after surgery and the presence of extra-abdominal metastases. The study included 1,290 patients from 25 institutions who underwent 1,344

Select Health

Cytoreductive Surgery (CRS) with Associated Hyperthermic Intraperitoneal Chemotherapy (HIPEC), continued

procedures between 1989 and 2007. HIPEC was performed in 1,154 procedures. Postoperative mortality was 4.1%. The principal origin of peritoneal carcinomatosis was pseudomyxoma peritonei in 301 patients. Median overall survival (OS) for patients with pseudomyxoma peritonei was not reached (median OS for all patients, 34 months).

In 2010, additional information about the subgroup of patients with pseudomyxoma peritonei was provided (Elias et al.). CRS was achieved in 219 patients (73%), and HIPEC was performed in 255 (85%). The primary tumor site was the appendix in 91% of patients, the ovary in 7%, and unknown in 2%. Tumor histology was disseminated peritoneal adenomucinosis in 51%, peritoneal carcinomatosis with intermediate features in 27%, and peritoneal mucinous carcinomatosis in 22%. Postoperative mortality was 4%, and morbidity 40%. Mean follow-up was 88 months. The 1-, 3-, and 5-year OS rates were 89.4%, 84.8%, and 72.6%, respectively. The 10-year survival rate was 54.8%. Median survival had not yet been reached but will exceed 100 months. Disease-free survival (DFS) was 56% at 5 years, and median duration of DFS was 78 months. A multivariate analysis identified 5 prognostic factors: extent of peritoneal seeding ($p=0.004$), institution ($p<0.001$), pathologic grade ($p=0.03$), sex ($p=0.02$), and use of HIPEC ($p=0.04$). When only the 206 patients with complete CRS were considered, the extent of peritoneal seeding was the only significant prognostic factor ($p=0.004$).

A report (Chua et al., 2009) of the long-term survival of 106 patients with pseudomyxoma peritonei treated between 1997 and 2008 with CRS and HIPEC and/or unheated intraperitoneal chemotherapy for 5 days postoperatively. Sixty-nine percent of patients had complete cytoreduction. Eighty-three patients (78%) had HIPEC intraoperatively, 81 patients (76%) had unheated postoperative intraperitoneal chemotherapy, and 67 patients (63%) had both. Seventy-three patients had disseminated peritoneal adenomucinosis, 11 had peritoneal mucinous carcinomatosis, and 22 had mixed tumors. Mortality rate was 3%, and severe morbidity rate was 49%. Median follow-up was 23 months (range, 0–140 months). Median OS was 104 months with a 5-year survival rate of 75%. Median progression-free survival (PFS) was 40 months with 1-, 3-, and 5-year PFS rates of 71%, 51%, and 38%, respectively. Factors influencing OS included histopathologic type of tumor ($p=0.002$), with best survival in patients with disseminated peritoneal adenomucinosis and worst survival in patients with peritoneal mucinous carcinomatosis. Factors influencing survival include histopathologic type of tumor, the use of both HIPEC and unheated postoperative intraperitoneal chemotherapy, completeness of cytoreduction, and severe morbidity.

Another study (Vaira et al., 2009) reported their experience managing pseudomyxoma peritonei with CRS and HIPEC in a single institution in 60 patients, 53 of whom had final follow-up data. The postoperative morbidity rate was 45%; no postoperative deaths were observed. The primary tumor was appendiceal adenocarcinoma in 72% of patients and appendiceal adenoma in 28%. Approximately half of the patients with adenocarcinoma had received previous systemic chemotherapy. Five- and 10-year OS rates were 94% and 85%, respectively, and 5- and 10-year DFS rates were 80% and 70%, respectively. Significant differences in improved OS were observed in patients who experienced complete surgical cytoreduction ($p<0.003$) and in those with histologic type disseminated peritoneal adenomucinosis versus those with peritoneal mucinous carcinomatosis ($p<0.014$).

In 2007, a systematic review (Yan et al.) of all relevant studies from 1996 to 2006 on the efficacy of CRS and intraperitoneal chemotherapy for pseudomyxoma peritonei. There were no randomized controlled trials (RCTs) or comparative studies. Ten studies were included (863 patients); all were uncontrolled, observational studies. Two studies had relatively long-term follow-up of 48 and 52 months, and median follow-up in the remaining studies was less than 3 years (range, 19–35 months). Median survival across all studies ranged from 51 to 156 months. One-, 2-, 3-, and 5-year survival rates varied from 80% to 100%, 76% to 96%, 59% to 96%, and 52% to 96%, respectively. Overall mortality rates varied from 0% to 18%, and morbidity from 33% to 56%.

In a retrospective cohort study (Lord et al., 2014), about 512 patients with perforated appendiceal tumors and pseudomyxoma peritonei who received CRS/HIPEC at a single center in the U.K. had achieved complete cytoreduction. Thirty-five (26%) of 137 patients who recurred underwent repeat CRS/HIPEC; median time to recurrence was 26 months. Complete cytoreduction was achieved (again) in 20 patients (57%). Mean OS in patients without recurrence (n=375), patients who recurred and had repeat CRS/HIPEC (n=35), and patients who recurred but did not have repeat CRS/HIPEC (n=102) was 171 months (95% CI, 164 to 178), 130 months (95% CI, 105 to 153), and 101 months (84 to 119), respectively (log-rank test, $p=0.001$). Five-year survival was 91%, 79%, and 65%, respectively. The incidence of complications was similar between primary and repeat procedures.

Cytoreductive Surgery (CRS) with Associated Hyperthermic Intraperitoneal Chemotherapy (HIPEC), continued

Large, retrospective cohort studies have consistently shown median and 5-year OS as 47 to 156 months and 41% to 96%, respectively, for patients with pseudomyxoma peritonei who are treated with CRS/HIPEC. One retrospective study of 26 patients who underwent CRS/HIPEC for recurrence indicated 5-year OS of 34%. Procedure-related morbidity and mortality have generally decreased over time to acceptable levels (16% to 49% and 0% to 4%, respectively, in recent studies).

Alexander et al. (2013) reported on 211 patients from 3 tertiary care centers in the United States who had malignant peritoneal mesothelioma and had undergone CRS/HIPEC. On multivariate analysis, factors statistically associated with a favorable outcome were aged younger than 60 years, complete or almost complete cytoreduction, low histologic grade, and HIPEC with cisplatin (rather than mitomycin-C). Shetty et al. (2014) similarly reported improved OS and reduced hospital stay with carboplatin HIPEC compared with mitomycin-C HIPEC in 44 patients with DMPM.

Metastatic Mesothelioma. For a 2011 systematic review, Baratti et al. searched the PubMed database from 1979 to 2010 for studies on the clinical management of diffuse malignant peritoneal mesothelioma (DMPM). The review included 14 studies with a total of 427 patients, 289 of whom underwent CRS with HIPEC, 2 with unheated intraperitoneal chemotherapy for 3–5 days postoperatively, and 106 with both. Studies that included patients with well-differentiated or low-grade types of mesothelioma were excluded. All included studies were prospective, uncontrolled case series. Mean patient age ranged from 49 to 56 years. All institutions used peritonectomy and multivisceral resection to remove visible disease. HIPEC protocols varied widely among institutions in terms of technique, drugs, carriers, timing, and temperature. Operative mortality and morbidity were reported in 11 monoinstitutional series. Operative mortality ranged from 0% to 10.5%. Overall, death occurred in 11 (3.1%) of 373 assessable patients. In one multi-institutional series, mortality was 2.2%. Morbidity (severe and life-threatening complications) varied from 20% to 41%. For patients who underwent CRS and HIPEC, median OS ranged from 29.5 to 92 months. Median OS was not reached in 3 series but exceeded 100 months in one of these. One-, 2-, 3-, and 5-year OS rates varied from 43% to 88%, 43% to 77%, 43% to 70%, and 33% to 68%, respectively. In 4 studies, median PFS ranged from 7.2 to 40 months. Results of a 2014 systematic review that included 7 studies published after the Baratti et al. review were aligned with these findings: Pooled 1-, 3-, and 5-year survival estimates were 84%, 59%, and 42%, respectively.

The largest study in both systematic reviews was a 2009 international registry study by Yan et al., for which 401 patients (99%) had complete follow-up. Of these patients, 92% received HIPEC. Reasons for not receiving HIPEC included unheated intraperitoneal chemotherapy for 5 days postoperatively being given instead, intraoperative hemodynamic instability, and unclear reason. Median and 1-, 3-, and 5-year survival rates were 53 months, 81%, 60%, and 47%, respectively.

The review acknowledged the possibility of patient selection bias as an explanation for the superior survival noted with aggressive treatment over more conventional treatment modalities, because patients with poor performance status are generally excluded from CRS and HIPEC. The authors concluded that, even in the absence of controlled data, the evidence suggests that the use of CRS and HIPEC in the treatment of DMPM should be the benchmark against which other treatments should be evaluated.

In the 2010 retrospective, multicenter cohort study described, the principal origin of tumor was peritoneal mesothelioma in 88 patients. Median survival for this group of patients was 41 months. Independent prognostic indicators in multivariate analysis were institution, origin of peritoneal carcinomatosis, completeness of CRS, extent of carcinomatosis, and lymph node involvement.

Retrospective cohort studies have shown median and 5-year OS of 30 to 92 months and 33% to 68%, respectively, for patients with peritoneal mesothelioma who are treated with CRS/HIPEC. Two studies indicated improved outcomes with platinum-containing HIPEC (cisplatin or carboplatin) compared with mitomycin-C. Procedure-related morbidity and mortality has remained relatively steady over time at approximately 35% and 5%, respectively.

Ovarian Cancer. Particularly, with regards to metastatic ovarian cancer, this has been determined to be feasible, but further studies are needed to determine the effects on survival. Chiva et al. found among patients with primary ovarian cancer who were treated with primary debulking and HIPEC, the weighted median overall survival was 37.3 months (range 27–78), the median disease-free survival was 14.4 months (range 12–30), and the 5-yr-survival rate was 40% (range 28–72). In the recurrent cohort, the overall survival after HIPEC was 36.5 months (range 23–62), and the median disease-free survival was 20.2 months (range 11–29). The rates of severe morbidity were 25% and 19% in the primary and

Cytoreductive Surgery (CRS) with Associated Hyperthermic Intraperitoneal Chemotherapy (HIPEC), continued

recurrent groups, respectively. They concluded, although randomized trials are ongoing, the recently published retrospective data regarding the use of HIPEC for primary advanced and for recurrent ovarian cancer do not indicate any apparent advantage of this treatment in terms of the survival outcomes in these patients. Therefore, HIPEC cannot be considered a standard treatment and should not be offered outside of clinical trials. Hotouras et al. performed a systematic literature review, with the conclusion that cytoreductive surgery and HIPEC seem to be associated with promising results in patients with recurrent ovarian cancer. Large international prospective studies are required to further quantify the true efficacy of HIPEC and identify the optimal treatment protocol for a maximum survival benefit. NCCN is silent on this treatment for ovarian cancer.

Colorectal Cancer. Particularly, for colon cancer, mixed results have been produced with regards to patient selection; some pointing to effectiveness, even with a high peritoneal cancer index. Another suggesting PCI > 15, appears to be a relative contraindication. In addition, per The American Society of Peritoneal Surface Malignancies (ASPSM), a recent recommendation was made on a standardized delivery of HIPEC in patients with colorectal cancer, which represents an important first step in enhancing research in this field. Studies directed at maximizing the efficacy of each of the seven key elements will need to follow. Per NCCN: The panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery and HIPEC to be investigational and does not endorse this therapy outside of a clinical trial.

One last consideration of note is the lack of recently published studies using newer agents such as bevacizumab (Avastin), cetuximab (Erbitux®), or panitumumab (Vectibix) as part of the treatment regimen. These agents could have a significant impact on survival, quality of life, and other outcomes with significantly less morbidity and mortality than older systemic chemotherapeutic agents and should also be compared to CRS with HIPEC or EPIC.

In conclusion, several case studies and a systematic review on the use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been published. Although no randomized trials or comparative studies have been published, data have shown consistent, long-term, disease-free survival, and overall survival with the use of this technique. Procedure-related morbidity and mortality have decreased over time. Because the prevalence of pseudomyxoma peritonei is very low, the conduct of high-quality trials is difficult. Therefore, based on the available evidence, CRS and HIPEC may be considered medically necessary for this indication.

Billing/Coding Information
Covered for the indications outlined above when criteria are met

96547	Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; first 60 minutes (list separately in addition to code for primary procedure)
96548	Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, including separate incision(s) and closure, when performed; each additional 30 minutes (list separately in addition to code for primary procedure)

Not covered: Investigational/Experimental/Unproven for this indication

CPT CODES

96549	Unlisted chemotherapy procedure

HCPCS CODES

No specific codes identified

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Cytoreductive Surgery (CRS) with Associated Hyperthermic Intraperitoneal Chemotherapy (HIPEC), continued

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Revision History

Revision Date	Summary of Changes
11/6/24	For Commercial Plan Policy, added criterion #2: "For patients with stage III ovarian cancer" as a qualifying factor for coverage of this procedure.
5/9/25	For Commercial Plan Policy, added criterion #3: "For patients diagnosed with metastatic colon cancer to the peritoneum, if the following are not present: biliary obstruction, extensive disease at the gastrohepatic ligament/porta hepatis, extensive retroperitoneal disease, intraparenchymal liver lesions (requiring major resection), diffuse small bowel serosa/mesenteric involvement, and/or multiple sites of small bowel obstruction" as a qualifying factor for coverage of this procedure.

Select Health

6/11/25	For Commercial Plan Policy, added new coverage criterion #4: "For patients diagnosed with gastric cancer, only with peritoneal carcinoma with a low PCI (≤ 10), and who are candidates to undergo complete cytoreduction; and who have completed at least 3 months of chemotherapy.

Select Health

Select Health

MEDICAL POLICY

GAMMATILE

Policy # 674

Implementation Date:10/05/23
Review Dates: 10/2/24
Revision Dates:

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Primary brain tumors are the most common tumors of the central nervous system (CNS) and are named based on the cell type from which they arise. They may be either benign or malignant. Gliomas, arising from the supporting brain cells known as glia, are the most common malignant tumor in adults. Gliomas are subdivided into astrocytomas, arising from the astrocytes; ependyomas, the malignant transformation of the ependymal cells in the ventricles of the brain; glioblastomas multiforme (GBM), invasive aggressive tumors comprised of various cell types; medulloblastomas, usually found in the cerebellum; and oligodendrogliomas, arising from the myelin cells.

Metastatic brain neoplasms (also referred to as brain metastases [BMs]) are tumors caused by cancer cells that spread from another part of the body to the brain and are associated with substantial morbidity, mortality, and treatment burden. Median survival for patients with BMs ranges from a few months to a few years, making timely treatment critical. However, the rate of local recurrence of a surgically resected BM is estimated to be as high as 85%. An estimated 20% to 40% of all patients with cancer in the United States have metastases to the brain. Patients with melanoma, lung cancer, breast cancer, and renal cell carcinoma are most likely to develop BM.

Symptoms of brain tumors include headaches, morning vomiting, seizures, personality changes, weakness, balance issues or gait abnormalities, excessive sleepiness, and changes in speech, vision, or hearing. Over 85% of all CNS tumors are brain tumors, with estimates of 24,810 new cases and 18,990 deaths from brain tumors and other CNS tumors in 2023. Management of brain tumors is complex and involves a multidisciplinary approach from neurosurgeons, medical and radiation oncologists, neurologists and neuroradiologists (National Comprehensive Cancer Network. Treatment options may include chemotherapy, surgical resection, radiation therapy, targeted therapy, active surveillance, and/or supportive therapy.

A novel form of localized radiation therapy is interstitial or intracavitary brachytherapy, which involves the placement of radiation implants directly into the tumor site. GammaTile (GT Medical Technologies Inc.) offers this localized therapy. GammaTiles are bioresorbable collagen tiles that contain 4 cesium-131 (a radioactive isotope) seeds. The implants (or seeds) are placed into the surgically created cavity following debulking of the brain tumor and are layered side by side until the cavity is filled.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health

GammaTile, continued

Select Health covers the use of GammaTile, only for recurrent Grade IV astrocytoma, and only when ALL the following criteria are met:

1. Patient has undergone initial maximal surgical resection with standard-of-care adjuvant therapy (concurrent Temodar plus 40-60Gy fractionated radiotherapy followed by adjuvant Temodar); and

2. Patient has recurrence of disease within the high-dose radiotherapy volume; and

3. Patient is not a candidate for a clinical trial; and

4. Patient is a candidate for resection of the recurrence within the high-dose radiotherapy volume.

Note: Gamma Tile will be only utilized within the resection cavity within the high-dose radiotherapy volume.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information
CPT CODES

77799 Unlisted procedure, clinical brachytherapy

Key References

1. Hayes, Inc. Clinical Research Response. GammaTile (GT Medical Technologies Inc.) for Brain Tumors. Jun 16, 2023.

Select Health

GammaTile, continued

Members may contact Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Coverage Policy may call Select Health Provider Relations at (801) 442-3692.

Select Health

Select Health

MEDICAL POLICY

HUMAN STEM CELL TRANSPLANTATION (HSCT), BONE MARROW TRANSPLANTATION (BMT)

Policy # 105

Implementation Date:7/98

Review Dates: 2/27/01, 11/21/01, 4/15/02, 1/30/04, 6/16/05, 6/22/06, 6//11/09, 2/17/11, 4/25/13, 2/20/14, 3/19/15, 2/11/16, 2/16/17, 2/15/18, 2/17/19, 2/17/20, 2/18/21, 6/15/22, 2/16/23, 5/29/24

Revision Dates: 4/22/02, 10/23/03, 1/27/04, 2/9/04, 7/6/04, 11/12/07, 7/29/08, 11/9/09, 1/6/10, 3/6/17, 6/16/22, 8/26/22, 1/11/23

Disclaimer:
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2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Bone marrow transplants (BMT), or more appropriately named human stem cell transplant (HSCT), in conjunction with high dose chemotherapy have become accepted practice for certain patients with specific cancers. Unless the member's certificate of coverage specifically excludes coverage, appropriate candidates who meet established criteria for this treatment are covered by Select Health.

High dose chemotherapy (HDC) involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, localized radiotherapy is also given, and is included in the term HDC when applicable. The most significant side effect of HDC is marrow ablation, and thus, HDC is accompanied by a reinfusion of stem cells in order to repopulate the bone marrow. The potential sources of stem cells are described below.

Donor Types

Autologous – Autologous stem cells may be harvested from the patient's bone marrow or peripheral circulation. Peripheral stem cells are harvested with one or more pheresis procedures. In order to mobilize the stem cells into the peripheral circulation, a course of chemotherapy or growth factors, or both may precede the pheresis procedures.

Syngenic – Syngenic stem cell support refers to stem cells harvested from the bone marrow or peripheral blood of an identical twin. The use of syngeneic stem cells is obviously limited by the rarity of identical twins.

Allogenic – Stem cells can be harvested from the bone marrow or peripheral circulation of a related or unrelated *donor*. Unlike peripheral autologous stem cells, the harvest of the peripheral stem cells is not preceded by a course of chemotherapy.

Blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogenic source, these stem cells are antigenically "naïve" and are thus associated with a lower incidence of rejection or graft vs. host disease.

Tandem Transplants – 2 planned courses of high dose chemotherapy and stem cell support are referred to as "tandem transplantation." Tandem transplants are typically administered at intervals of 2−6 months, contingent on recovery from prior toxicity.

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers human stem cell transplantation (HSCT) when either A or B are met:

A. Procedure is recommended, endorsed, and performed by Intermountain Transplant Services; **OR**

B. For all other clinicians, **Select Health covers these procedures only *for the specific indications below when the following general conditions are met***. All other uses of human stem cell transplantation meet the plan's definition of investigational/experimental.

Patients being considered candidates for bone marrow transplants must meet all the following criteria for the procedure to be considered as covered:

1. The patient meets disease state age limit restrictions, except when a syngeneic donor is available.
2. Current, standard chemo/radiation therapy is not likely to be curative or to prevent progressive disability or death.
3. After completion of the HSCT, the patient has a reasonable expectation to return to "normal" activities of daily living.
4. The patient does not have an additional progressive disorder, which would otherwise seriously jeopardize survival independent of the underlying malignancy, e.g., severe heart failure or COPD.
5. An approved HSCT center has evaluated the patient and has recommended a HSCT.

Medical conditions for which human stem cell transplantation may be covered are as follows:

1. Acute leukemias (AML, ALL, or AUL)
2. Amyloidosis
3. Chronic lymphocytic leukemia (CLL)
4. Chronic myelogenous leukemia (CML) [including subtypes]
5. Ewing's Sarcoma for patients under the age of 18 with no existing disease at time of transplant
6. Germ cell cancer
7. Glioblastoma (in pediatric population only)
8. Hodgkin's lymphoma
9. Hereditary immunodeficiency disease (including severe combined immunodeficiency disease, Wiskott-Aldrich syndrome, Leukocyte adhesion deficiencies, Kostmann's syndrome [infantile agranulocytosis])
10. Myelodysplastic syndrome
11. Mucopolysaccharidoses (e.g., Hunter's, Hurler's Sanfilippo, Maroteaux-Lamy variants) in patients who are neurologically intact)
12. Mucolipidoses (e.g., Gaucher's disease, metachromatic leukodystrophy, globoid cell leukodystrophy, adrenoleukodystrophy) for patients who have failed conventional therapy (e.g., diet, enzyme replacement) and who are neurologically intact
13. Multiple myeloma
14. Neuroblastoma (PNET tumors except for ependymoma)
15. Non-Hodgkin's lymphoma
16. Osteopetrosis (Albers-Schoenberg disease or marble bone disease)
17. Severe aplastic anemia refractory to other medical treatments
18. Thalassemia major
19. Wilm's tumor (in pediatric population only)

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

20. X-linked dymphoproliferative syndrome

Autologous hematopoietic stem cell transplantation is covered for systemic sclerosis/scleroderma when all the following criteria are met:

a) Adult patients < 60 years of age; and
b) Maximum duration of condition of 5 years; and
c) Modified Rodnan Scale Scores >15; and
d) Internal organ involvement*; and
e) History of < 6 months treatment with cyclophosphamide; and
f) No active gastric antral vascular ectasia; and
g) Patients do not have any exclusion criteria (see below)**

**Patients with internal organ involvement indicated by the following measurements should not be considered for autologous HCT:

- Cardiac: left ventricular ejection fraction < 50%; tricuspid annular plane systolic excursion < 1.8 cm; pulmonary artery systolic pressure > 40 mm Hg; mean pulmonary artery pressure > 25 mm Hg
- Pulmonary: DLCo < 40% of predicted value; FVC < 45% of predicted value
- Renal: creatinine clearance < 40 ml/minute.

Autologous hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma not meeting the above criteria is considered investigational.

Medical conditions for which human stem cell transplantation is *NOT* covered, include, but are not limited to the following conditions:

1. Autoimmune disease including systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis
2. Breast cancer
3. Ependymoma
4. Osteosarcoma
5. Ovarian epithelial cell carcinoma
6. Renal cell cancer or other solid organ malignancies
7. Retinoblastoma
8. Rhabdomyosarcoma

Coverage for allogenic HSCT also requires the patient to meet all the following conditions:

1. All 6 major HLA antigens match between the designated donor and the recipient, except for pediatric patients receiving umbilical cord blood
2. The patient and donor cells are non-reactive in mixed leukocyte cultures

Coverage of autologous HSCT also requires the patient to meet all the following conditions:

1. Patients are in a disease phase where peer-reviewed literature has demonstrated that autologous HSCT is beneficial compared to non-transplant therapy.
2. No sign of end organ dysfunction which significantly increases the risk associated with performing a HSCT
3. Patient has adequate harvested and stored stem cells

Select Health

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

Coverage of Donor Lymphocytes:

Select Health considers donor lymphocyte infusion (DLI) medically necessary for persons who have a prior allogeneic bone marrow or peripheral stem cell transplantation.

Select Health covers serial/double transplants (only applies when two transplants are initially planned) *when the following conditions are met*:

- For multiple myeloma (MM) patients *ONLY:*
  1. Patient has not been classified as high-risk as defined by mSMART criteria:
     - FISH
       - ♦ Del 17p
       - ♦ t(4;14)
       - ♦ t(14;16)
     - Cytogenic deletion 13
     - Cytogenic hypodiploidy
     - PCLI ≥ 3%
  2. Patient did not achieve a complete response (CR)* or very good partial response (VGPR)† after initial transplantation.

     * *Complete response (CR): Negative immunofixation on the serum, AND disappearance of any soft tissue plasmacytomas, AND ≤ 5% plasma cells in bone marrow*[173]

     † *Very good partial response (VGPR): Serum and urine M-protein detectable by immunofixation but not on electrophoreses, OR*

     90% or greater reduction in serum M-protein plus urine M-protein plus urine M-protein level is less than 100mg per 24 hours[173]

- For all other conditions:
  - Subsequent or repeat HSCT on the same patient requires separate justification and consideration as a covered benefit. Documentation of the reasons for the failure of the initial graft(s) and presentation of evidence-based literature establishing the potential for success with repeat transplantation is required.

Select Health covers tandem HSCT only in the following conditions. All other conditions are considered investigational and not covered.

Covered Indications for Tandem HSCT:

1. **Neuroblastoma in patients with high risk* of recurrence defined by INRGSS criteria.**

*High risk is defined as:

1. L1 disease with amplified *MYCN* marker in any age group
2. L2 disease in patient ≥18 months with poorly differentiated or undifferentiated disease and amplified *MYCN* marker
3. M stage disease under age 18 months with amplified *MYCN* marker
4. M stage disease ≥18 months of age
5. MS Stage disease <18 months of age with amplified *MYCN* marker
6. MS stage disease <18 months of age with 11q Aberration on genetic testing

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage,

Select Health

please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Acute Lymphocytic Leukemia

In childhood, all conventional chemotherapy is associated with complete remission rates of about 95% with long-term remission rates of 60%. Therefore, in patients with a first complete remission, high dose therapy is considered necessary only in those with risk factors predictive of relapse. These factors include:

- Age greater than 15 years
- Leukocyte count greater than 10 x 10−9L
- Extramedullary disease, particularly CNS
- Chromosomal abnormalities, including Philadelphia chromosome

The prognosis after first relapse is related to the length of the original remission. For example, there is 40%−50% leukemia-free survival for children whose first remission was longer than 3 years, compared to only 10%−15% of those with early relapse. Thus high-dose chemotherapy may be a strong consideration in those with short remissions. At the present time, the comparative outcomes using high dose therapy with either autologous or allogenic stem cell are unknown.

The policy on adults ALL, is in part, based on a 1997 BCBSA TEC assessment that specifically focused on the use of high dose chemotherapy and autologous (not allogenic) stem cell support. This assessment offered the following conclusions:

- In patients in first complete remission, the data suggest equivalent survivals after high dose therapy and autologous stem cell support compared to conventional chemotherapy. In this setting, the decision between high dose chemotherapy and conventional chemotherapy reflects a choice between an intensive therapy of short duration and a considerably longer but somewhat milder treatment.
- In other settings, such as in second or subsequent remissions, there were inadequate data to determine the relative effectiveness of autologous bone marrow transplant compared to conventional chemotherapy.

While high dose chemotherapy and allogenic stem cell support may be considered an option in some adults, the increased morbidity and mortality related to graft vs. host disease, particularly in an older population, are serious limitations. In addition, unlike acute myeloid leukemia, there does not appear to be a beneficial graft vs. leukemia effect to counterbalance the increased mortality of the procedure. Finally, adults with AML treated with allogenic transplant tend to fail because of treatment-related mortality and failure is rarely related to relapse. In contrast, in ALL, even for adults who survive the procedure, there is a significant relapse rate, and overall very few adults are long-term disease-free survivors. For these reasons, allogenic transplant remains controversial as a treatment of adult ALL and may be routinely recommended only in the very poor risk subgroup of those with ALL in association with the Philadelphia chromosome or in patients with refractory or relapsed ALL.

A 2000 TEC assessment focused on high-dose chemotherapy and allogeneic stem cell support after a prior failed course of high-dose chemotherapy and autologous stem cell support, in the treatment of a variety of malignancies, including ALL. The TEC assessment found that there were insufficient data to permit conclusions about this treatment strategy.

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

A January 2003 search of the literature revealed no new published clinical studies presenting data that would result in a change to the policy criteria. Hallbook and colleagues published results of a multicenter study of 153 adult patients with previously untreated ALL who received induction chemotherapy with high dose cytarabine, cyclophosphamide, daunorubicin, vincristine and betamethasone. The median age was 42 years. A complete response rate was achieved in 90% of patients younger than 60 years and 70% in patients older than 60 years. The estimated three-year overall survival was 29%. As in previous studies, patients with predominantly B-cell expression and age less than 40 years experienced a continuous complete response rate at three years of 62%.

Acute Myelogenous Leukemia

High dose chemotherapy has been investigated in three general settings, either as consolidation therapy after first complete remission, as salvage therapy after first relapse or second complete remission, and to treat primary refractory disease.

Post-Remission Therapy
In patients in first complete remission, high dose chemotherapy with allogenic stem cell support (HDC/AlloSCS) has been shown to decrease the leukemic relapse rate, but at the price of increased treatment-related morbidity and mortality. This raises the question of whether allogenic transplant offers any real benefit as a post-remission strategy in patients in first complete remission. Furthermore, it is unclear whether the outcomes associated with high dose therapy are better compared to those associated with other non-marrow ablative dose intensification strategies, such as high dose cytarabine (ara-C). Therefore, at the present time, high dose chemotherapy with allogenic stem cell support is typically reserved for those patients with high-risk features. These factors include AML secondary to prior chemotherapy and/or radiotherapy for another malignancy, AML proceeded by a myelodysplastic syndrome, presence of circulating blasts at the time of diagnosis, difficulty in obtaining first complete remission, or leukemias with monocytoid differentiation (FAB classification M4 or M5). Certain cytogenetic abnormalities are also associated with a poor prognosis, such as abnormalities of chromosome 12, deletions of chromosomes 5 and 7, or trisomy of chromosome 8. In contrast, chromosomal abnormalities with a good prognosis include translocations between chromosome 8 and 12 and 15 and 17, or an internal derangement of chromosome 16. Older age range of AML in general and the lack of availability of a suitable donor may limit the use of allogenic stem cell support.

The ideal allogenic donors are HLA-identical siblings, matched at the HLA-A, B and DR histocompatibility loci. Related donors mismatched at one locus are also considered suitable donors. A matched unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently there has been interest in haploidentical donors, i.e., a parent or a child of the patient, where typically there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of graft vs. host disease and overall morbidity of the procedure may be severe, and experience with these donors is limited.

The overall survival after high dose chemotherapy and autologous stem cell support (HDC/AuSCS) is similar to that associated with allogenic stem cell support from HLS matched donors. The decreased treatment-related mortality of autologous stem cell support is counterbalanced by the increased relapse rate due to the lack of a beneficial graft vs. leukemia effect. Similar to allogenic stem cell support, it is not clear if high dose chemotherapy with autologous support results in improved outcomes compared to conventionally dosed chemotherapy or high dose cytarabine.

Refractory AML
Twenty to 40% of patients with AML will not achieve remission with conventionally dosed chemotherapy, i.e., refractory AML. HDC/AlloSCS using a matched related or unrelated donor can cure a subset of these patients. For patients who lack a suitable donor, alternative treatments include salvage chemotherapy with high-dose cytarabine or etoposide-based regimens, monoclonal antibodies (e.g., gemutuzumab ozogamicin), multidrug resistance modulators, and investigational agents.

Relapsed AML
A total of 50%−70% of patients with are expected to relapse after attaining a first complete remission. Conventional chemotherapy is generally not curative once relapse occurs, even if a second complete remission can be achieved. High dose chemotherapy with either allogenic or autologous stem cell support is associated with a prolonged disease-free survival in 30%−40% of patients in first relapse or second complete remission. Due to the mortality associated with remission induction, high dose chemotherapy

with allogenic stem may be considered as the initial treatment of relapsed disease. In patients without an allogenic donor, or who are not candidates for allogenic stem cell support due to age or other factors, high dose chemotherapy with autologous stem cell support may be considered after a second complete remission. (Due to contamination of stem cell populations by malignant cells, autologous stem cells are typically harvested only when the patient is in remission.) Alternatively, HDC may be used for initial therapy of relapsed disease if autologous stem cells were stored at the time of first complete remission.

A 2000 BCBSA TEC assessment focused on high-dose chemotherapy and allogenic stem cell support after a prior failed course of high-dose chemotherapy and autologous stem cell support, in the treatment of a variety of malignancies, including AML. The BCBSA TEC Assessment found insufficient data to permit conclusions about this treatment strategy. A small series of pediatric patients (n = 23) treated in this fashion has been published since that Assessment. The study reports nine of twenty-one AML patients surviving after HDC/AlloSCS, but also reports an equal proportion of deaths from regimen-related toxicity.

A literature search conducted in October 2003 did not identify any additional recent randomized studies comparing high-dose chemotherapy with autologous or allogenic stem cell support and standard dose chemotherapy. Accordingly, there is no evidence to suggest a change to any of the policy criteria. This position was reinforced by discussions in two recent reviews. Several randomized trials have been published; however, these compared outcomes using stem cells, with or without growth factors, or compared two or more HDC regimens.

A search of the National Cancer Institute (NCI) clinical trial database (PDQ) in October 2003 identified three ongoing randomized trials in the United States that involve stem-cell support for patients with AML. The first randomizes patients to standard or novel conditioning regimens followed by allogenic SCS (protocol RPCI-RP-9815); the second randomizes patients to daunorubicin and cytarabine with or without gemutuzumab ozogamicin, followed by autologous or allogenic SCS (protocol E-1900); and the third randomizes patients to induction chemotherapy with or without PSC 833 (an investigational drug), followed by intensification with high-dose chemotherapy/peripheral blood stem cell support or conventional-dose chemotherapy (protocol CLB-19808).

It has been generally accepted that patients with “favorable risk” AML based on cytogenetics should not undergo an HSCT in CR1. Patients with an AML containing the cytogenetic abnormality Inv(16) in the past would not be considered for HSCT in CR1 because they had a 60%−70% chance of being cured with upfront chemo. New technologies have found that a minority of these patients in addition to the Inv(16) also have a mutation in their c-kit gene. The c-kit gene encodes a tyrosine kinase receptor (KIT) that is required in normal spermatogenesis and is expressed in seminomas and dysgerminomas, a subset of human germ cell tumors (GCTs). If they are positive, they have a poor prognosis (20%−30% chance of cure) and should be transplanted in CR1. This is only the beginning of a future ability to predict who is likely to be cured with upfront chemotherapy, and who are not, based on molecular technologies.

Aplastic Anemia

Aplastic anemia (AA) is a stem cell disorder resulting in abnormal development of subsequent blood cell populations. The disorder can arise as a congenital form (e.g., Fanconi's anemia) or be secondary to exposure to environmental toxins, ionizing radiation, or cytotoxic drugs. Clinical manifestations include progressive fatigue, weakness, pallor, and hemorrhage. Congenital forms are also commonly associated with abnormalities such as renal hypoplasia, hyperpigmentation, and bone dysplasia.

Three degrees of severity of aplastic anemia are recognized: moderate, severe, and very severe. Severe AA is classified as platelets less than 20 x 109 /Liter, granulocytes less than 0.5 x 109 /Liter, and reticulocytes less than 1% after correction for hematocrit. Very severe AA is classified the same as for severe AA but with granulocytes less than 0.2 x 109 /Liter. Moderate AA includes cases that show abnormal platelet, granulocyte, and reticulocyte counts less severe than those of severe AA.

Moderate AA is typically treated with supportive care. This includes removal of the etiologic agent where possible, steroid therapy (androgens), specific antibiotics targeted against documented infections, broad-spectrum antibiotics in the presence of severe neutropenia, and shielding from potential infections. (Transfusions may be necessary, but are generally used cautiously and sparingly, due to potential for alloimmunization, which lessens probability of good outcome with human stem cell transplantation).

There are two treatment alternatives for severe and very severe AA: allogenic human stem cell transplant (HSCT) or anti-thymocyte globulin (ATG). The outcome of allogenic HSCT from an HLA-matched donor and ATG treatment are comparable in terms of overall survival with rates of 70%−90% at five to ten years.

A 1992 TEC Assessment concluded that patients who do not have an HLA-matched donor and who have failed ATG have approximately 25%−40% disease-free survival 1−7 years following treatment with allogenic bone marrow transplant from an HLA-mismatched donor. Outcome was related to degree of mismatch with the probability of disease-free survival after bone marrow transplant outweighing the risk of early death from treatment-related causes only for donors mismatched at one HLA locus.

Since the earlier studies, results from allogenic HSCT have improved over time owing to a variety of factors such as use of cytokine-primed peripheral stem cells; progressive modification of conditioning regimens and lower treatment related mortality; improved transfusion support and antibiotic regimens; and the introduction of cyclosporine in the graft versus host disease regimen. Graft rejection and graft-versus-host disease are the major complications of allogeneic HSCT in AA. However, intensification of the immunosuppressive regimens with cyclosporine and/or ATG or total body irradiation or lymphoid irradiation has reduced the risk of graft rejection. Several hospital registries are now reporting 5-year survival rates following allogenic HSCT as high as 89%. Out of all of the studies and registries has evolved a most favorable subgroup of patients achieving survival rates of over 90%. This favorable subgroup includes young patients, un-transfused or minimally transfused, and uninfected. Based on the body of evidence and evolving practice it is apparent that allogenic HSCT with an HLA matched donor is considered the standard of care in aplastic anemia, particularly in children and adults with severe, aggressive aplastic anemia. The literature currently describes immunosuppressive therapy with anti-thymocyte globulin as an alternative therapy for such patients who are not candidates for allogenic HSCT because of failure to find a suitable matched donor.

Astrocytomas and Gliomas

Diffuse fibrillary astrocytomas are the most common type of brain tumor in adults. These tumors are classified histologically into three grades of malignancy, grade II astrocytoma, grade III anaplastic astrocytoma, and grade IV glioblastoma multiforme. Oligodendrogliomas are diffuse neoplasms that are clinically and biologically most closely related to the diffuse fibrillary astrocytomas. However, these tumors have generally better prognoses than diffuse astrocytomas with mean survival times of 10 years. In addition, oligodendrogliomas appear to be more chemosensitive than other types of astrocytomas. Glioblastoma multiforme is the most malignant stage of astrocytoma, with survival times of less than 2 years for most patients.

Treatment of primary brain tumors focuses on surgery, either with curative intent or optimal tumor debulking. Surgery may be followed by radiation therapy and/or chemotherapy. Survival after chemoradiotherapy is largely dependent on the extent of residual tumor after surgical debulking. Therefore, tumors arising in the midline, basal ganglia, or corpus callosum or those arising in the eloquent speech or motor areas of the cortex, which typically cannot be extensively resected, have a particularly poor outcome. Treatment of children less than 3 years is complicated by the long-term effects of radiation therapy on physical and intellectual function. Therefore, in young children, CNS radiation is avoided whenever possible.

An update of the 1994 TEC Assessment reviewed literature published through 1999 and confirmed the Assessment's conclusions. It noted that although there was much research interest in use of HDC for glioblastoma multiforme due to its uniformly poor prognosis, the published literature was relatively scant, consisting primarily of single-institution case series. The following representative examples were cited.

Bouffet and colleagues reported on a series of 22 children and young adults with high-grade gliomas treated with high dose chemotherapy and autologous stem cell support. The response rate was 29% with one complete and three partial responses. However, the authors concluded that survival with high dose chemotherapy was no better than that reported with conventional treatments. Heideman and colleagues reported on a case series of 13 pediatric patients with bulky disease or recurrent disease treated with high dose chemotherapy and radiotherapy. While the overall response rate was 31%, the authors similarly concluded that overall survival was no better than conventional treatment regimens. Finlay and colleagues reported on a 1996 case series of 45 children and young adults with a variety of recurrent CNS tumors, including gliomas, medulloblastomas, ependymomas, and primitive neuroectodermal

tumors. Of the 18 patients with high-grade gliomas, the response rate was 29%. The median survival of this group was 12.7 months. Of the 5 long-term survivors, all had high-grade glioma with minimal residual disease at the time of high dose chemotherapy. Based in part on these results, the authors recommend aggressive surgical debulking before high dose chemotherapy is even considered.

Studies focusing on the use of high dose chemotherapy in adults with glioblastoma multiforme report results similar to those in children, i.e. high dose chemotherapy appear most successful in those with minimal disease at the time of treatment, with an occasional long-term survivor. Cairncross and colleagues treated 20 adults with chemosensitive oligodendrogliomas with high dose thiotepa followed by autologous stem cell transplant. Four patients (20%) died of treatment related toxicities; 4 had complete response and 16 had a partial response. Four patients (20%) are alive and tumor-free at a median 31 months after high dose thiotepa. The authors considered the results to be disappointing.

However, researchers agreed that Phase III trials are needed to confirm these preliminary findings, particularly to control for patient selection bias. For example, because of the morbidity and mortality of high dose chemotherapy, candidates for this aggressive therapy were typically in better physical condition with a better prognosis than the overall group of patients with the disease. Therefore, the evaluation of high dose therapy should ideally have included a control group for comparison, since any survival benefit associated with high dose chemotherapy could be related to the improved prognosis entirely independent of any effect of high dose chemotherapy. There were no controlled trials published through mid-1999.

A 1999 search of the National Cancer Institute database on ongoing clinical trials (PDQ database) identified 3 phase II trials in adult patients with brain tumors that included high dose chemotherapy; two of the studies focused on oligodendroglioma and one focused on glioblastoma multiforme or brain stem tumors. One phase II study was identified focusing on children less than 10 years old with newly diagnosed malignant brain tumors. This study included children with malignant gliomas as well as medulloblastomas or other tumors derived from neuroectodermal cells. There were no phase III studies identified.

The literature was searched again in February 2002 and November 2002 for studies published since 1999. The searches discovered few new reports, and those identified did not change the conclusions of the 1994 BCBSA TEC Assessment or the policy statement. A review by Brandes et al. concluded that the high drug doses used in this treatment caused excessive toxicity that was not balanced by a significant improvement in survival. Similarly, Levin et al. concluded it was presently unclear whether HDC and autologous stem cell support have a place in management of cerebral gliomas. Additional reports on small, uncontrolled series of patients with pontine gliomas recurrent oligodendrogliomas, or those undergoing radiation therapies for high-grade gliomas also did not suggest that this treatment improves survival.

An updated literature search in November 2003 identified no new published clinical trials of HDC plus autologous stem cell support for the treatment of gliomas. Therefore, the policy criteria are unchanged.

A repeated search of NCI's PDQ database in November 2003 identified 3 relevant open trials for adult patients. The first is a Phase I study of temozolomide, thiotepa, and carboplatin followed by infusion of autologous peripheral blood or bone marrow stem cells for patients with newly diagnosed or recurrent high-grade brain tumors with minimal residual disease following irradiation. The second is a Phase II study of high-dose thiotepa followed by infusion of autologous peripheral blood stem cells for adults or children with malignant glioma. The third is also a Phase II study of thiotepa, carmustine, and etoposide followed by infusion of autologous peripheral blood stem cells in patients with CNS malignancies. This study also is open to patients with germ cell or primary neuroectodermal tumors, medulloblastoma, or CNS lymphoma. The search identified one additional Phase I/II study of temozolomide followed by infusion of autologous peripheral blood stem cells for children with newly diagnosed malignant glioma or recurrent CNS or other tumors. The search did not identify any Phase III trials.

Autoimmune Disease

The medical community is most familiar with the use of high dose chemotherapy with autologous stem cell support (from here on referred to as AuSCS) as a treatment of non-marrow-based malignancies. In this situation the scientific rationale for the high dose chemotherapy was clear -- the targeted tumor showed a steep dose response curve such that higher doses of chemotherapy would result in increased tumor cell kill with ultimate cure. In this setting the marrow ablation was considered a lethal side effect

unless treated with reinfusion with autologous stem cells. For marrow-based malignancies, such as multiple myeloma or chronic lymphocytic leukemia, reinfusion of autologous stem cells always carried the risk of reinfusion of the malignant stem cells. In all these situations, targeted tumor cells represented a single clone of malignant cells.

The scientific rationale for the use of AuSCS in autoimmune diseases is not as clear-cut as in oncologic applications. For example, the pathogenesis of autoimmune diseases is not precisely known. While the immunologic component is undisputed, there is no readily identifiable pathogenic clone of cells. It is not clear whether the disorder is related to an abnormal stem cell, or whether the disorder is related to a pathogenic clone of more mature lymphocytes, or whether the disorder is related to immune dysregulation. However, interest in high dose therapy was initially stimulated by the observation that patients with autoimmune diseases treated with high dose therapy and allogenic stem cell transplant for other reasons (frequently therapy related to secondary aplastic anemia) often enjoyed prolonged remission of their autoimmune disease. Nevertheless, the use of allogenic stem cells is not practical in many patients due to the lack of an available donor and the older age of most patients with autoimmune diseases.

The initial experience with AuSCS in patients with autoimmune disease involved several individual case reports of patients with autoimmune diseases that were principally being treated for a co-existing malignancy. As reviewed by Snowden, the early data suggest that AuSCS may result in initial remissions, but relapses are common. In this country Burt and colleagues at Northwestern University in Chicago have reported the largest experience. In 1998, Burt and colleagues reported on a case series of 10 patients, including 6 with multiple sclerosis, 2 with SLE, and 2 with rheumatoid arthritis. All patients had progressive disease refractory to standard treatment. Stem cells were collected from either the marrow or peripheral blood. Stem cells were enriched ex vivo by CD34+ selection (CD34+ cells permit positive selection of the critical stem cell and exclusion of potentially pathogenic T-cells). All patients received high dose chemotherapy. In addition, the patients with MS received total body irradiation in order to ablate lymphocytes sequestered in the CNS. All 6 patients with MS enjoyed stabilization of their disease, both patients with SLE had no evidence of active disease after transplant, and the patient with rheumatoid arthritis improved. Median follow up period was 11 months. The authors state that the reason for post-transplant disease stabilization is unclear. One hypothesis posits that post-transplant there is a prolonged period of relative immunosuppression, which may function to reset the balance between tolerance and autoimmunity. The authors also state that longer-term follow up is necessary to determine the duration of response, and that randomized controlled trials are needed.

Clearly the experience with AuSCS for autoimmune diseases is preliminary in nature. Additional research will need to address the following challenges:

- Until there is a solid scientific rationale for the treatment effect of AuSCS, evidence will have to rely solely on empiric trials. Given the unpredictable waxing and waning course of many autoimmune diseases, randomized trials will be important.
- Numerous technical issues remain notably the role of T cell depletion among the harvested stem cell. However, the role of T cells in different stages of disease is not precisely known.
- Patient selection criteria are difficult. Ideally, the best use of AuSCS may be in those patients with prognostic factors reliably predictive for progressive refractory disease, before the onset of irreversible organ damage. For example, many patients with SLE or scleroderma might not be candidates for AuSCS due to co-existing renal failure that increase the morbidity of high dose regimens.
- Final health outcome data may be difficult to define. For example, outcomes of multiple sclerosis are often evaluated with the Kurtzke EDSS (extended disability status scale). This scale is weighted toward ambulatory status and does not reflect improvements in other outcomes such as incontinence or upper extremity function. Some studies of MS have used serial MRI scans to detect new brain lesions as an alternative.
- The definition of a successful final health outcome is unclear. Will AuSCS be used for curative intent? Absent complete cure, would the risk benefit ratio suggest that partial remission with reduction in steroid dosage is a successful outcome?

- While the use of AuSCS is evolving, new therapies are emerging for autoimmune diseases, particularly rheumatoid arthritis. Therefore, the outcomes with non-marrow ablative therapies may be improving.

This policy is also supported by a 2000 BCBSA TEC assessment that concluded there was inadequate scientific evidence to permit conclusions. Specifically, the published evidence consists of case reports of single case studies describing a variety of outcomes in a total of 71 patients with at least 12 different autoimmune diseases. The BCBSA TEC assessment concluded that due to the general complexity of the autoimmune disease and the wide variations in disease activity among patients with the same disease and in any one patient at various points in time, scientific evidence must be designed that examines an adequate number of patients in each disease category and that applies sufficiently standardized patient selection criteria, disease severity stratification, and clinical outcomes measurement. The case reports currently available for analysis do not adequately address these issues. The BCBSA TEC Assessment was updated in 2001, focusing on high-dose lymphoablative therapy both with and without autologous stem-cell rescue. The BCBSA TEC Assessment noted registry data suggest that the outcomes of high-dose therapy with stem cell rescue, as a treatment of autoimmune disease does not have predictable and always favorable results. Overall, approximately 10% of the patients die from the procedure. There are relatively little data regarding high-dose lymphoablative therapy without stem-cell rescue. One trial was terminated prematurely due to apparent excess morbidity in the treatment arm.

Breast Cancer

The 1996 BCBSA TEC Assessment reviewed 12 studies with a total of 459 patients. These included:

- A trial from South Africa (published in 1995 and discredited in 2001 because of scientific misconduct) that randomized patients not previously treated for metastatic breast cancer to HDC/AuSCS or to conventional-dose therapy;
- A crossover trial (still published only as an abstract) that randomized complete responders after induction chemotherapy to immediate consolidation with HDC/AuSCS or to HDC/AuSCS delayed until relapse; and
- 10 uncontrolled series.

The assessment also reviewed registry data showing marked decreases in transplant-related mortality between 1992 and 1994 that were attributable to improvements in supportive care and the shift from bone marrow to mobilized peripheral blood progenitors as the source of hematopoietic stem cells. The (now discredited) South Africa trial reported longer survival for patients in the HDC arm (median 1.7 years), although survival in the conventional treatment arm (median 0.9 years) was shorter than reported with conventional regimens most commonly used in the United States. The crossover trial reported longer disease-free survival (medians, 0.85 vs. 0.32 years) but shorter overall survival (medians, 1.7 years vs. 3.2 years) in the immediate than in the delayed HDC arm. When combined with results of uncontrolled trials, the balance of evidence available in 1996 suggested HDC/AuSCS yielded survival durations at least equivalent to those after conventional-dose therapy. Although acute treatment-related morbidity was more severe, the duration of therapy was much shorter with HDC/AuSCS. Since available evidence was insufficient to determine whether outcomes of either treatment alternative were superior, patients were encouraged to seek this treatment in the context of continued clinical trials.

In the 1998 BCBSA TEC Assessment for high risk primary (Stage II/III) breast cancer, evidence was reviewed comparing HDC/AuSCS with conventional-dose chemotherapy for adjuvant treatment, included:

- Two small randomized trials (39−41 patients per arm), a case-control study (60 patients per group), and 6 uncontrolled series (combined n = 302) of patients with ten or more positive lymph nodes;
- Two uncontrolled series (combined n = 116) on patients with 4−9 positive nodes; and
- Three uncontrolled series (combined n = 86) on patients with non-metastatic inflammatory breast cancer.

For patients with 10 or more positive nodes, the two randomized trials (1 published as an abstract) reported 60%−70% survival at 5 years, with no statistically significant differences between treatment arms. The case-control study and the uncontrolled series suggested longer duration of overall and

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disease-free survival than in previous studies of conventional-dose adjuvant therapy in patients with ten or more positive nodes. However, the case-control study only matched for a subset of known risk factors. Also, patients treated with HDC/AuSCS in uncontrolled series were generally younger and had better performance status than those given conventional-dose adjuvant therapy. Thus, the analysis could not exclude contributions of patient selection bias to outcome differences. Consequently, the technology assessment criteria were not met because conclusions could not be made concerning the effectiveness of HDC/AuSCS for the treatment of stage II/III breast cancer in patients with ten or more positive lymph nodes. HDC/AuSCS also failed to meet the technology assessment criteria for patients with 4−9 positive lymph nodes or those with inflammatory breast cancer, since the lack of controlled studies, small sample sizes, and inadequate follow-up did not permit conclusions.

In May 1999, highly publicized results were presented from randomized trials of HDC for metastatic breast cancer (2 studies) and adjuvant therapy of high-risk primary breast cancer (3 studies).

The PBT-1 trial randomized patients with a complete or partial response to induction therapy for previously untreated metastatic breast cancer to HDC/AuSCS (n = 101) or to conventional-dose maintenance chemotherapy (n = 83) for up to 2 years. Median survival (24 months vs. 26 months) and overall survival at 3 years (32% vs. 38%) did not differ between arms. There also were no statistically significant differences between arms in time to progression or progression-free survival at 3 years. While treatment duration was substantially shorter for those randomized to HDC/AuSCS, acute morbidity was markedly more severe than after conventional-dose maintenance.

PEGASE-04, a small (total n = 61) French randomized trial for patients with chemotherapy-sensitive metastatic breast cancer, reported a significantly longer median duration of progression-free survival for those in the HDC arm (27 vs. 16 months; p = 0.04). The median duration of overall survival also was longer in the HDC arm, although this difference was not statistically significant (36 vs. 16 months; p = 0.08).

Preliminary results of a CALGB/Intergroup trial for patients with 10 or more positive nodes did not show statistically significant survival differences between the HDC and conventional chemotherapy arms. However, these data were not yet sufficiently mature, since the designated endpoint of the trial required a 5-year follow-up and this interim analysis was based on a median follow-up of 37 months. A Scandinavian Breast Cancer Study group trial on patients with 8 or more positive nodes also reported no significant differences in event-free or overall survival between the HDC and conventional arms at a median follow-up of 24 months. However, the control arm in this study received an individualized and dose-escalated regimen with higher cumulative doses than those in the HDC arm. This "tailored" regimen increased the combined incidence of secondary leukemia and myelodysplasia. The South African study for high-risk patients with 10 or more positive nodes was unique in reporting improved median relapse-free survival in the HDC arm. However, this trial also was unique since all patients were treated with HDC immediately without initial conventional-dose adjuvant chemotherapy. [Note also that this trial was discredited in 2000 based on evidence of scientific misconduct] All 3 trials reported higher incidences of severe non-lethal toxicity in the HDC arms. Also, no data were reported from ongoing randomized trials for patients with 4-9 positive lymph nodes.

Further review of the medical literature from 1999−2002 revealed some additional information on the efficacy of HDC with stem cell transplant for both metastatic and high-risk primary breast cancer. Of the 2 trials presented at ASCO in 1999, only the PBT-1 trial has been published as a peer-reviewed journal article. Published results confirm those reported at the meeting. However, some reviewers criticized this trial since few partial responses were converted to complete responses in the high-dose arm, and since only a minority of those enrolled was subsequently randomized. Of 553 patients enrolled and given initial induction therapy, only 310 achieved a partial (n = 252) or complete (n = 58) response and only 199 were randomized. Of 72 partial responders assigned to the HDC arm after initial induction therapy, only 5 (7%) were converted to complete responses.

The 1995 South African study reviewed in the 1996 BCBSA TEC assessment was audited in 2001 and discredited for scientific misconduct. Two additional trials were reported at ASCO meetings in 2000 and 2001 but are available only as abstracts. A small crossover study, limited to women who did not progress after induction therapy for bone-only metastases, reported modest improvements in progression-free survival (but no effect on overall survival) from immediate compared with delayed HDC/AuSCS. A larger Canadian randomized trial without crossover reported interim results at 19 months median follow-up. In

this analysis, progression-free survival was longer (but overall survival was equivalent) for those randomized to HDC/AuSCS. However, grade 3/4 toxicities were more common after HDC/AuSCS. Definitive conclusions require longer follow-up and analysis of final outcomes from this ongoing study.

Of 3 trials presented at the 1999 ASCO meeting, only the Scandinavian study has been published as a peer-reviewed article. Published results confirm those reported in the meeting presentation. Although an update was presented at the 2001 ASCO meeting, the CALGB/Intergroup trial has not yet published final outcomes. A small pilot from the Netherlands with 81 patients randomized to HDC/AuSCS or conventional-dose therapy and a median of 7 years follow-up reported no differences in overall or disease-free survival at 5 years. Several larger randomized trials, including the National Cancer Institute (NCI) sponsored study for patients with 4−9 positive nodes, have completed accrual and are continuing to follow patients. Although several of these trials have reported interim results as meeting presentations, reviewers generally agree that definitive conclusions require final analyses and peer-reviewed publications.

Note also that results still are unavailable from randomized trials comparing HDC/AuSCS with conventional-dose chemotherapy for adjuvant or neoadjuvant therapy of inflammatory breast cancer. A search of the NCI's PDQ® database for open trials (last searched in 10/2002) showed 3 open Phase II trials and no open Phase III trials for these patients.

Several uncontrolled pilot or Phase II trials have reported results after 2 or 3 sequential cycles of HDC/AuSCS for patients with metastatic, high-risk operable or inflammatory breast cancer. However, data are unavailable from studies that directly compare outcomes of tandem transplants with those of either single transplants or conventional-dose regimens.

Available data was inadequate to evaluate outcomes of HDC/AlloSCS in the treatment of breast cancer. Although several uncontrolled studies subsequently were published on use of non-myeloablative conditioning regimens for allotransplants, data are lacking from controlled trials. Furthermore, evidence is scant for an immunologic graft-versus-tumor effect after allotransplants for breast cancer. The1999 BCBSA TEC Assessment found inadequate data regarding the use of HDC/AlloSCS as a salvage therapy after a failed prior course of HDC/AuSCS. The literature search conducted for the 2002 update did not identify any reports that might change the conclusion of the 1999 BCBSA TEC Assessment.

Chronic Myelogenous Leukemia

This policy was initially based on a 1986 BCBSA TEC assessment that addressed the use of allogeneic stem cell transplant as a treatment of chronic myelogenous leukemia and a 1994 BCBSA TEC assessment that addressed the use of autologous stem cell transplant. The 1986 assessment concluded that allogeneic stem cell transplant met the TEC criteria. Since that time, allogeneic transplant has emerged as the standard treatment of CML when a suitable stem cell donor is available. It is estimated that chronic phase patients receiving an HLA-matched sibling donor transplant have a 45%−75% probability of long-term disease-free survival, while those transplanted with more advanced disease have a 15%−40% long-term survival. Young, good risk patients transplanted early in chronic phase from HLA-matched but unrelated donors reportedly have a 40%−60% probability of long-term survival, although it is lower than that of similar patients transplanted from matched sibling donors. With the availability of imatinib mesylate, allogeneic transplants may be used less often to manage patients with CML, or they may only be used when a complete molecular response to the drug fails or is not achieved. These uncertainties will be resolved only after additional clinical studies and longer follow-up than presently available.

Obvious limitations of allogeneic stem cells are the lack of a suitable donor for many patients and the increased morbidity of allogeneic transplant in older patients. An obvious limitation of the use of autologous stem cells is the near certainty that leukemic cells will be transfused back into the patient. The 1994 BCBSA TEC assessment concluded that autologous stem cell transplant did not meet the TEC criteria. However, it is recognized that many CML patients still have normal marrow stem cells, and research has focused on ways to isolate and expand this normal clone of cells. Techniques used have included ex vivo purging, long-term culture and immunophenotype selection. Even without such techniques, there have been isolated case reports of partial cytogenetic remissions after high dose chemotherapy with autologous stem cell support, and one study suggests that patients undergoing such therapy may have improved survival compared with historical controls. A 1994 article summarized the results of 200 consecutive autologous transplants using purged or unpurged marrow from 8 different

transplant centers. Of the 200 patients studied, 125 were alive at a median follow up of 42 months. Of the 142 transplanted in chronic phase, the median survival had not been reached at the time of publication, while the median survival was 35.9 months for those transplanted during an accelerated phase. Other data consists of small single institution case series using a variety of techniques to enrich the population of normal stem cells among the harvested cells.

A November 2002 updated literature search on autologous transplantation also found no comparative trials, but identified several new reports from small, uncontrolled studies with a total of 182 patients (range: 15−41 patients) given autotransplants for CML. Patient populations varied across these studies. Some focused on newly diagnosed patients or those in the first year since diagnosis. Others focused on patients who did not respond to or relapsed after initial treatment using interferon alpha. Finally, some focused on patients transplanted in late chronic phase or after transformation to accelerated phase or blast crisis. Although some patients achieved complete or partial molecular remissions and long-term disease-free survival, these studies do not permit conclusions free from the influence of patient selection bias. Note also that all autotransplanted patients included in these reports were treated before imatinib mesylate (Gleevec) became available. Since this drug has been shown to induce major hematologic and, less often, cytogenetic remissions even among patients in accelerated phase and blast crisis, future studies of autotransplants for CML, may focus on patients who fail or become resistant to imatinib mesylate. Alternatively, it may be incorporated into combination regimens used for high-dose therapy.

Allogeneic human stem cell transplantation results in the lowest incidence of leukemic relapse. Disease-free survival rates using allogeneic transplantation in first complete remission have ranged from 45%−60%. The use of allogeneic human stem cell transplantation as primary post remission therapy is limited by the need for a human leukocyte antigen (HLA)-matched sibling donor and the increased mortality from allogeneic human stem cell transplantation of patients who are older than 50 years. The mortality from allogeneic human stem cell transplantation that uses an HLA-matched sibling donor ranges from 20%−40%, depending on the series. The use of matched, unrelated donors for allogeneic human stem cell transplantation is being evaluated at many centers but has a very substantial rate of treatment-related mortality, with disease-free survival rates less than 35%. Retrospective analysis of data from the International Bone Marrow Transplant Registry suggests that consolidation chemotherapy does not lead to an improvement in disease-free or overall survival for patients in first remission undergoing allogeneic bone marrow transplant from an HLA-identical sibling.

Additional literature concerning second transplants was reviewed. Two patient series document preliminary outcomes of a second allogenic stem cell transplant following high dose chemotherapy for acute and chronic leukemias are available in abstract form only. Together 18 patients with chronic myelogenous leukemia received a second allogenic stem cell transplant following a failed autologous transplant or a failed allogenic transplant. Long term outcomes are not available. Further study is needed in order to reach conclusions concerning the safety and efficacy of a second high-dose hematopoietic stem cell transplant for CML.

Consolidating a first Clinical Remission (CR)

Several randomized trials compared outcomes of autotransplants used to consolidate a first CR in patients with intermediate or aggressive NHL, with outcomes of an editorial (16), the preponderance of evidence showed that consolidating first CRs with a stem-cell transplant did not improve overall survival for the full population of enrolled patients. However, a subgroup analysis at 8 years median follow-up focused on 236 patients at high- or high-intermediate risk of relapse (based on age-adjusted IPI scores) who were enrolled in the largest of these trials (the LNH87-2 protocol; reference 12). The subgroup analysis reported superior overall (64% vs. 49%; relative risk 1.51, p = 0.04) and disease-free survival (55% vs. 39%; relative risk 1.56, p-0.02) for patients at elevated risk of relapse who were consolidated with an autotransplant.

A large, multi-group, prospective, randomized phase III comparison of these strategies (the S9704 trial) is ongoing, to confirm results of the subgroup analysis in a larger population with diffuse large B-cell lymphoma at high- and high-intermediate risk of relapse. Nevertheless, many clinicians view the LNH87-2 subgroup analysis as sufficient evidence to support use of autotransplants to consolidate a first CR when risk of relapse is high. In contrast, editorials and recent reviews agree that available evidence shows no survival benefit from autotransplants to consolidate first CR in patients with intermediate or aggressive NHL at low- or low-intermediate risk of relapse (using age-adjusted IPI score). Similarly, evidence

remains insufficient to support routine use of transplants to consolidate a first CR for any patients with indolent (follicular) lymphomas.

Ependymoma

Initial treatment of ependymoma consists of maximal surgical resection followed by radiotherapy. Chemotherapy typically does not play a role in the initial treatment of ependymoma. However, relapse of ependymoma is common, typically occurring at the site of origin. Treatment of recurrence is problematic; further surgical resection or radiation therapy is usually not possible. Given the poor response to conventional dose chemotherapy, high dose chemotherapy has been investigated as a possible salvage therapy. At the present time, published literature regarding high dose chemotherapy for ependymoma consists primarily of small case series. For example, Mason and colleagues reported on a case series of 15 patients with recurrent ependymoma. Five patients died of treatment related toxicities, 8 died from progressive disease and 1 died of unrelated causes. After 25 months, 1 patient remains alive, but with tumor recurrence. The authors concluded that their high dose regimen of thiotepa and etoposide was not an effective treatment of ependymoma. Grill and colleagues similarly reported a disappointing experience in 16 children treated with a thiotepa-based high dose regimen.

A November 2003 updated search of the literature failed to identify any new data on outcomes of HDC with autologous stem cell support for patients with ependymoma. A separate literature search for data on HDC with allogenic stem cell transplant also revealed no published data for PNETs or ependymoma.

A search of the NCI's clinical trial database in November 2003 did not identify any trials of HDC specifically focused on ependymoma. However, patients with ependymoma were eligible to participate in several trials enrolling patients with a variety of malignant brain tumors.

Ewing's Sarcoma

Ewing's sarcoma was originally thought to be a sarcoma due to its origin in the bone, most commonly the femur. However, the recently discovered neuroepithelial origin has prompted its reclassification. (While considered a solid tumor of childhood, Ewing's sarcoma could also be categorized as a primitive neuroectodermal tumor (PNET). Poor risk factors for Ewing's sarcoma include a large primary tumor greater than 8 cm in diameter, pelvic location, or metastases at diagnosis.

Ewing's sarcoma is considered a chemosensitive disease and therefore there has been interest in using high dose chemotherapy as initial treatment of metastatic Ewing's sarcoma, or for salvage therapy for relapsed or refractory Ewing's sarcoma, where conventional chemotherapy has had very limited success. Most high dose regimens have focused on melphalan with or without additional radiation therapy. In a summary of the data, Chen reported that for patients with recurrent or refractory disease, high dose chemotherapy produced a complete remission in about one third of patients. Although many of these complete responses were short lived, a small subset of patients may become long-term survivors. The European Bone Marrow Transplant Solid Tumor Registry has reported on outcomes of 210 patients receiving high dose chemotherapy for treatment of residual disease. The complete response rate was 27%, with an overall 5-year survival rate of 19%.

High-dose chemotherapy has also been studied as a consolidation treatment of patients with high-risk tumors. The European Bone Marrow Transplant Solid Tumor Registry has reported on outcomes of 63 patients with high risk Ewing's sarcoma in either first or second complete remission who were treated with high dose chemotherapy and autologous stem cell support. In this study, patients presenting with metastases constituted the high-risk group. Patients treated at the time of first complete remission had a 5-year disease-free survival of 21%, while those treated during a second complete remission had a 5-year disease-free survival of 32%. Although these results may appear to be superior to those associated with historical controls, the patient selection criteria for those in the registry is unknown. The largest Phase II studies of high dose chemotherapy in this population of patients have been undertaken by the National Cancer Institute. Over a 5-year period, 91 patients were enrolled in one of three protocols consisting of induction chemotherapy, radiation to the primary site, total body irradiation followed by high dose chemotherapy with autologous stem cell support for those who responded to the initial induction therapy. In this highly selected population, 30% survived long term without progression of their disease. While this outcome was better than expected, patient selection bias could explain any effect. A number of other Phase II studies have been performed over the past 20 years, characterized by small numbers of patients, a variety of regimens including different combinations of drugs and radiotherapy, and a variety of

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patient selection criteria. While many reported promising results, no randomized studies have been performed to control for the patient selection bias in any of these studies.

A January 2002 updated search of the literature revealed one new study of HDC/AuSCS in patients with Ewing's sarcoma. Meyers and colleagues treated 23 patients with newly diagnosed, metastatic Ewing's sarcoma who responded to induction chemotherapy with high dose melphalan, etoposide, and total body irradiation followed by stem cell support. Two-year event free survival was 24%. Three patients died from toxicity to the high dose regimen. The authors concluded that consolidation with this high dose regimen failed to improve the probability of event free survival in patients with newly diagnosed, chemosensitive, metastatic Ewing's sarcoma.

A July 2008 brief M-Tech review found a number of articles included patients > 18 years of age in their study sample, very few reported separate or comparative outcomes by age cohort. Thus, while multiple studies infer some benefit from stem cell transplantation in conjunction with HSCT in disease free and overall survival, these results are aggregated across all ages and comparative efficacy of this treatment in patients is difficult to determine in a statistically valid manner. This lack of adult specific information is primarily due to the small sample size in most studies. Given the low incidence of this cancer, none of the studies were powered sufficiently to permit group comparisons of any sort.

Though separate studies focusing specifically on adults are limited, a number of studies provided tables with outcomes listed by patient, which permits some limited comparisons by age group. **Table 1** presents mortality data culled from various studies for children and adults who underwent stem cell transplantation in conjunction with high dose chemotherapy.

Table 1 Mortality Data for patients age < 18 and over age 18

Study	Adult Mortality	Child Mortality	Follow-up
Burdach, et al. (2000)	11/11 (100%)	15/24 (63%)	5 years
Fraser, et al. (2006)	2/3 (67%)	6/13 (46%)	3.5 years
Kasper, et al. (2004)	30 months (survival) (n = 7)	47 months (survival) (n = 1)	
Ladenstein, et al. (1995)	3/6 (50%)	9/17 (53%)	5 years
Yamada, et al. (2007)	8/14 (57%)	1/3 (33%)	3 years

Multiple studies included age at time of diagnosis or treatment as a factor in univariate or multivariate regression models predicting outcomes. Oberlin et al., for example, included 97 patients (median age at diagnosis: 12.3 years; range: 2 months to 25 years). Of these, 36% were older than age 15 at the time of diagnosis. Several factors had univariate associations with overall survival (OS) and event-free survival (EFS), but the multivariate analysis identified 3 independent prognostic factors for EFS: age 15 years or older, fever at diagnosis, and bone marrow involvement at diagnosis. Five-year EFS of patients ≤15 years was 46% vs. 21% for older patients ($p \leq 0.001$), and 5-year OS of patients ≤ 15 years was 49% versus 20% for older patients. In Burdach et al. (2000), among 11 adults and 24 children/adolescents, the only factor significantly influencing outcome was age ≥ 17 years, with older patients experiencing deteriorated outcomes. Likewise, in Burdach et al.'s 2003 study of 32 children and 22 adults, age ≥ 17 years at initial diagnosis significantly deteriorated outcomes. In Barker et al. survival did not differ between age ≤ 13 (n = 27) and > 13 years (n = 28). Kolb et al. found age at diagnosis to be a univariate predictor of survival but did not remain significant when included in a multivariate model.

A few studies included adult samples. Nath et al. followed 17 adult patients over a 4-year period. There was no transplant-related mortality. Two patients remained disease free beyond 4 years but the median progression free survival and overall survival following for the entire cohort was only seven months. In Englehardt 35 consecutive adult patients had a median follow-up of 100.6 months after transplantation. At follow-up, 11 patients were alive, with 9 in sustained complete remission and each one in partial remission and stable disease. Median overall survival was 17.1 months. In Laurence et al. follow up of 46 patients (median f/u = 7.1 years), 5-year overall survival and progression-free survival were 63 +/- 7.7% and 47 +/- 7.6%, respectively. Comparisons between these and outcomes for children are limited due to the substantial heterogeneity in sample composition and treatment protocols across studies. Outcomes from these studies cannot be directly compared with those including children only.

In summary, data on use of stem cell transplantation in patients ≤ 18 and older than 18 years of age are limited and inconsistent. Variation in patient definitions and treatments used limit the comparisons that can be made across trials. A prospective, randomized trial is needed.

Germ Cell Tumors

This policy is based on a 1991 BCBSA TEC assessment updated with literature published in the intervening period. The 1991 BCBSA TEC assessment offered the following conclusions:

- Data were insufficient to permit conclusions about the outcomes of high dose therapy and autologous stem cell support as initial therapy in patients with poor risk tumors, or after a first relapse following initial standard dose chemotherapy.
- Data demonstrated that, compared with conventional chemotherapy, outcomes after high dose chemotherapy and autologous stem cell support are improved in patients with germ cell tumors in second or subsequent relapse.

The intervening literature since 1991 does not change these conclusions. The most thorough review, published in 1999, is provided by Sobecks and Vogelzang. This review pooled the results of 6 studies that focused on high dose therapy as initial treatment of germ cell tumors. Only 2 of the studies reported survival data, and it was not clear whether the long-term survival is better than conventional therapy for comparable patients. Sobecks and Vogelzang pooled the results of 5 small studies that focused on high dose therapy as a treatment of germ cell tumors at first relapse. The continuous complete response was 56% with an estimated median duration of 29 months. The treatment related mortality was 5%. In contrast conventional dose chemotherapy can achieve 5-year disease-free survival of 30% and treatment related mortality of 2% or less. Given that high dose chemotherapy carries a higher risk of initial treatment related mortality, it is important to compare the long-term survival outcomes of conventional vs. high dose therapy.

The data published since 1991 also supports the beneficial effect of high dose chemotherapy and autologous stem cell support in patients with germ cell tumors in second or subsequent relapse, as concluded by the 1991 BCBSA TEC assessment.

There have been scattered reports of the use of tandem courses of high dose chemotherapy. However, there are no controlled studies that demonstrate that the outcomes of tandem transplants are superior to those of a single course of high dose chemotherapy.

Finally, a 1999 BCBSA TEC assessment focused on the use of high dose chemotherapy and allogenic stem cell support as a salvage treatment for germ cell tumors after a failed autologous stem cell transplant. An initial thorough review of the published literature, and a 2002, updated review, identified no references describing this application of high dose therapy.

Hodgkin's Lymphoma

Initially, this policy was based on a 1987 BCBSA TEC Assessment focusing on high dose therapy and autologous stem cell support and a 1990 BCBSATEC Assessment focusing on allogenic stem cell support. Both concluded that there were adequate data to confirm an improved survival for relapsed disease compared to standard therapy. Allogenic stem cell support may be preferred over autologous stem cells when the relapse occurs in the bone marrow.

A 2000 BCBSA TEC assessment focused on high-dose chemotherapy and allogenic stem cell support after a prior failed course of high-dose chemotherapy and autologous stem cell support, in a variety of malignancies, including Hodgkin's disease. The TEC assessment found that there were inadequate data to permit conclusions about this treatment strategy.

A review of the literature conducted in November 2002 identified four randomized trials on patients with Hodgkin's disease. Only 1 of these studies compared outcomes of conventional dose chemotherapy with outcomes of high-dose chemotherapy plus stem-cell support. Entered into the trial were 166 patients with relapsed Hodgkin's disease. Patients were randomized at entry to conventional dose therapy (Dexa-BEAM; dexamethasone, carmustine, etoposide, cytarabine, and melphalan) or HDC with autologous stem-cell support (BEAM-AuSCS). After randomization, patients underwent two cycles of Dexa-BEAM; responding patients then proceeded to two more courses of Dexa-BEAM or to BEAM-AuSCS. With a median follow-up of 39 months, freedom from treatment failure was significantly better after HDC than after conventional-dose chemotherapy. Subgroup analyses showed improved survival after transplant for

patients treated in early first relapse (less than 12 months), late relapse (greater than 12 months), and a second or subsequent relapse. No difference was reported for overall survival; although such a difference might become apparent with longer follow-up (median survival had not been reached in either arm).

Although the duration of the first remission remains a strong prognostic factor predicting outcome of both conventional and high-dose therapy for relapse, there is consensus across recent authoritative reviews, historical cohort comparisons, and clinical series that patients treated with high-dose therapy tend to fare better overall than those managed with conventional dose regimens, regardless of the duration of remission. Therefore, the policy statement is changed and now suggests that HDC may be considered medically necessary for any patient with relapsed Hodgkin's disease, regardless of the length of remission.

The updated literature search identified few reports on outcomes of HDC with stem-cell support for upfront treatment of Hodgkin's disease, or to consolidate a complete response to initial induction therapy. These were all uncontrolled clinical series and are inadequate to permit conclusions. In addition, the literature was inadequate to permit conclusions regarding the role of HDC with allogenic stem-cell support as a treatment of Hodgkin's disease relapsing after HDC with autologous stem-cell support.

Homozygous Beta-Thalassemia

Thalassemia is a group of inherited disorders of hemoglobin metabolism common to the peoples of the central Mediterranean and central Africa. Clinical severity can range from minimal in individuals who are heterozygous carriers of the trait for alpha-thalassemia (i.e., thalassemia minor), to fatal anemia or fatal sequelae of cardiac iron deposits in homozygous beta-thalassemia (i.e., thalassemia major, Cooley's anemia). Treatment for thalassemia is typically supportive: transfusions, splenectomy, and use of medications that increase mobilization and excretion of iron deposits. Promising results have been seen with parenteral administration of desferoxamine, an iron chelator.

The policy for homozygous beta-thalassemia is based in part on a 1988 TEC Assessment which found that 65% of 173 patients reported in the literature with homozygous beta-thalassemia treated with allogeneic bone marrow transplant survive up to 34 months with sustained engraftment and no need of further therapy. Although transfusions and desferoxamine administration can extend life expectancy they are not curative, and the disease will be eventually fatal. Allogeneic bone marrow transplant appeared to be curative in 65% of beta-thalassemia patients.

A January 2002 updated search of the literature reveals several recent published series documenting survival rates of 86%, 94% and in mismatched donors 75%.

Lysosomal Storage Disorders

Lysosomal storage disorders are a heterogeneous group of diseases resulting from inherited defects in specific enzymes. Lysosomal enzymes function to degrade by-products of cellular metabolism. Deficiencies in these enzymes lead to accumulation of cellular material which damage end organs resulting in a wide spectrum of clinical symptoms. Some of the more typical manifestations include liver and spleen enlargement, skeletal deformities, corneal clouding, and demyelinating neuropathy. The disorders are progressive and usually fatal. The mucopolysaccharidosis lysosomal storage disorders include Hurler's, Sanfilippo, and Maroteaux-Lamy variants. Examples of the mucolipidoses lysosomal storage disorders include Gaucher's disease, metachromatic leukodystrophy, and adrenoleukodystrophy.

A 1992 TEC Assessment concluded that bone marrow transplant, when successful, results in sustained production of the deficient enzyme. The enzyme is delivered in adequate amounts to the visceral organs, namely the liver, spleen and skeletal system. Some enzyme may be delivered to the central nervous system, but this delivery is limited by the blood-brain barrier and occurs in much smaller quantities than in the other organs. The abnormal cells in the liver, spleen and bone marrow are cleared over a matter of months to a year preventing further damage. But damage to the CNS may continue to occur, although at a slower rate. HSCT does not appear to be a cure for these disorders, but successful HSCT appears to significantly alter the natural history of these disorders. The chance of a good outcome is best with HSCT early in the course of the disease. According to the published literature, transplantation in advanced disease nearly always results in a poor outcome.

Myelodysplastic Syndrome

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

Myelodysplastic syndrome (MDS) refers to a heterogeneous group of clonal hematopoietic disorders characterized by impaired maturation of hematopoietic cells and a tendency to transform into acute myelocytic leukemia (AML). MDS can occur as a primary (i.e., idiopathic form), or be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40%−60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome (i.e., trisomy 8). The most widely accepted classification system for MDS is the French-American-British (FAB) system that identifies 5 types of MDS with increasing numbers of circulating blast cells as follows:

- Refractory anemia (RA)
- Refractory anemia with ringed sideroblasts (RARS)
- Refractory anemia with excess blasts (RAEB)
- Refractory anemia with excess blasts in transformation (RAEBT)
- Chronic myelomonocytic leukemia (CMML)

Patients either succumb to disease progression to AML or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

Myeloproliferative Disorders

The myeloproliferative disorders are characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. Myeloproliferative disorders include the following:

- Polycythemia vera (PV) is characterized by an expansion of the total red cell mass. Initial treatment focuses on phlebotomy to reduce red cell mass and viscosity. However, the disease inevitably progresses and after a median survival of 15 years, patients typically succumb to thrombotic complications or leukemic evolution.
- Essential thrombocythemia (ET) is characterized by an isolated expansion of the megakaryocytic lineage. The median survival is 10 years with most deaths due to thrombotic complications.
- Agnogenic myeloid metaplasia with myelofibrosis, also known as primary myelofibrosis is characterized by marrow fibrosis, splenomegaly and extramedullary hematopoiesis.
- Chronic myeloid leukemia.

Given the long natural history of myelodysplastic syndrome, high dose chemotherapy is typically considered in those with increasing number of blasts, signaling a possible transformation to acute myeloid leukemia. Subtypes falling into this category include refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, or chronic myelomonocytic leukemia.

Patients with refractory anemia with or without ringed sideroblasts may be considered candidates for high dose chemotherapy when chromosomal abnormalities are present or the disorder is associated with the development of significant cytopenias (e.g., neutrophils less than 500/mm^3, platelets less than 20,000/mm^3).

Patients with myeloproliferative disorders may be considered candidates for high dose chemotherapy when there is progression to myelofibrosis, or when there is evolution toward acute leukemia. In addition, high dose chemotherapy may be considered in patients with essential thrombocythemia with an associated thrombotic or hemorrhagic disorder.

This policy is based in part on a 1992 BCBSA TEC assessment that focused on high dose chemotherapy and allogenic stem cell support as a treatment of myelodysplastic syndrome. The following conclusions were offered:

- High dose chemotherapy appears to improve health outcome of selected patients with MDS. The largest study showed an overall survival of 45% at three years.
- Compared to conventional therapy, consisting of supportive therapy, survival after high dose therapy can be considered at least as good.

A January 2002 updated search of the published literature reveals similar outcomes reported in recent clinical trials of high-dose chemotherapy and allogenic stem cell support for myelodysplastic syndrome.

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

The following summarizes the recent literature regarding high dose chemotherapy for myeloproliferative disorders:

> Due to the prolonged natural history of both polycythemia vera or essential thrombocythemia disorders and older average age of onset (60 years), high dose chemotherapy with allogenic stem cell support has not been extensively studied in these patients. A 1998 review reported only 9 patients with PV had been treated with high dose chemotherapy. However, considering that PV represents an emerging malignant clone of cells, and the success of high dose chemotherapy in other hematopoietic disorders, it seems reasonable to extrapolate the results of high dose chemotherapy for myelodysplastic syndrome to PV. There has been more research in agnogenic myeloid metaplasia (AMM, also called myelofibrosis) since this disorder may also occur in children. In addition, the short median survival of AMM compared to other myeloproliferative disorders has prompted earlier consideration of high dose chemotherapy. Of the total 29 patients reported in the literature, 16 patients were alive without evidence of relapsed disease between 7 months and 15 years after transplant.

An October 2003 literature search did not reveal new published studies of allogenic stem cell transplant that would alter the policy criteria as written.

Multiple Myeloma-High Dose Chemotherapy and Autologous Stem Cell Transplant

Single Transplant

The policy on high dose chemotherapy with autologous stem cell support as treatment for multiple myeloma is based on a 1996 BCBSA TEC assessment that specifically looked at patients with newly diagnosed, responsive multiple myeloma or refractory or resistant myeloma. Responsive myeloma is defined as tumors achieving a complete or partial (at least 50% tumor reduction) response to chemotherapy; while resistant or refractory multiple myeloma is defined as those tumors achieving a less than 50% reduction in tumor burden. The following conclusions were offered:

Newly Diagnosed or Responsive Multiple Myeloma

- The available data support the conclusion that high dose chemotherapy with autologous stem cell support is at least as effective and may be more effective than conventional dose chemotherapy for improving the health outcomes of the above patients. In a key randomized trial, the outcomes of high dose therapy were clearly better than conventional chemotherapy.

Resistant or Refractory Multiple Myeloma

- In contrast, insufficient data were available to support a conclusion regarding the outcomes of high dose chemotherapy and autologous stem cell support in patients with refractory myeloma. Most of the data consisted of uncontrolled clinical series of patients. In a December 2001 updated search of the literature one new published non-randomized phase II study in 36 patients with primary resistant or relapsed multiple myeloma were treated with HDC AuSCS. The probability of overall survival at 5 years was 27.3%. Median survival was 31 months. No randomized controlled trials have been reported.

The policy regarding tandem transplantation is based on 2 1998 BCBSA TEC assessments, focusing on tandem transplants for newly diagnosed or responsive multiple myeloma and resistant multiple myeloma. The following conclusions were offered:

Newly Diagnosed or Responsive Multiple Myeloma

- Only 5 published studies were found that provided data on the outcomes of treatment in patients receiving tandem transplant. Although one of the studies is a randomized study, the available data are still preliminary and do not permit conclusions on survival. The University of Arkansas has reported an extensive non-randomized single-institution case series of multiple myeloma treated with tandem transplant, however, the data compared results to historical controls treated with conventional-dose regimens and not to a single cycle of HDC/AuSCS, considered the gold standard for comparison.
- When using the previously published outcomes of patients receiving a single cycle of HDC/AuSCS as historical controls, the BCBSA TEC assessment found considerable overlap in the results reported for tandem and single transplant for nearly all the outcomes of interest. These

data were considered inadequate to permit conclusions regarding the health benefits associated with tandem transplant. Data on the duration of survival after tandem transplant are scant and nearly all other outcomes data are only available from single-arm studies with highly selected patients. Thus, the comparison of outcomes is subject to a high degree of patient selection bias.

Refractory or Resistant Multiple Myeloma

Two reports with a total of 69 patients treated at one institution and a third report with 30 patients provided the only data on the outcomes of tandem transplant for treatment of resistant multiple myeloma. There was no control group for direct comparison of outcomes in the most updated reports on the larger series of highly selected patients. The earlier report from this institution and the third paper included non-randomized control groups, but aggregated outcomes for patients with resistant myeloma and those transplanted as part of first-line therapy. In addition, insufficient detail was provided to determine if the patients given tandem transplant for resistant myeloma were sufficiently comparable to those given either single high dose chemotherapy or conventional dose salvage therapy to permit conclusions based on indirect comparison of outcomes from separate studies.

Serial Transplant

For the purpose of this policy, tandem transplants are 2 *planned* HSCT transplants regardless of the outcome of the initial transplant.

The Medical Technology Committee reviewed serial transplants in October 2009 and found a 2006 Hayes report on high dose chemotherapy in conjunction with stem cell transplantation for MM. The report gave a 'B' rating to tandem transplantation when used as first-line therapy for MM and a 'D' rating when used as salvage therapy. A 'B' rating indicates "some proven benefit" reflecting a moderate level of positive published evidence regarding safety and efficacy supports use of the technology for the cited application(s). Further research is required to fully clarify clinical indications, contraindications, treatment parameters, comparison with other technologies, and/or impact on health outcomes.

A 2009 meta-analysis from Kumar et al. evaluated the benefits of serial autologous stem cell transplant relative to a single transplant. The authors located 6 randomized controlled trials meeting inclusion criteria. The authors noted significant heterogeneity in outcomes reported in the literature. Though the response rate was significantly better for serial transplant, there was no incremental improvement in survival or event free survival. Moreover, tandem transplant conferred a higher risk for treatment related mortality.

Seven studies met criteria. Two of these were randomized controlled trials. Attal et al, for example, randomly assigned 399 previously untreated MM patients to single or serial transplants. Both groups first underwent high dose chemotherapy followed by stem cell transplantation. The probability of surviving event-free for 7 years after the diagnosis was 10% in the single-transplant group and 20% in the serial group ($p = 0.03$). The estimated overall 7-year survival rate was 21% in the single-transplant group and 42% in the double-transplant group ($p = 0.01$). Even in patients who did not have a good response to treatment within 3 months, the probability of survival at 7 years was 11% and 43% in the single and serial groups, respectively. Cavo et al. randomly assigned 321 patients with MM in similar fashion. Relative to the single group, serial transplantation resulted in better median relapse-free survival (24 vs. 42 months, respectively; $p < .001$), and significantly median extended event-free survival (23 vs. 35 months, respectively; $p = .001$).

In a nonrandomized study by Corso et al. 153 newly diagnosed MM patients were consecutively enrolled in a high-dose chemotherapy program including 2 serial autotransplants separated at 3 and 6 months. Though the percent of good responses (complete and very good partial responses) increased from 33%−91% after 2 transplants, there was no improvement in event-free survival or overall survival. Vesole et al. reported on 496 patients with MM who underwent a second transplant 5 months after the first one, on average. Treatment-related mortality during the first year after transplantation was 7%, and complete remission (CR) was obtained in 36%; the median durations of event-free survival and overall survival after transplant were 26 and 41 months, respectively.

Overall, the literature is somewhat equivocal in the outcomes reported. It is important to note, however, that the randomized studies located for this study suggested that the treatment is more effective than single transplant, while non-randomized studies were less likely to find benefits from this treatment. As these are small studies, additional replication is needed to demonstrate that the benefits observed in the

randomized trials are reliable. Nevertheless, the literature suggests that the treatment is feasible and effective in treating MM.

Multiple Myeloma-High Dose Chemotherapy and Allogenic Stem Cell Transplant

The policy on high dose chemotherapy and allogenic stem cell support is based on a 1996 BCBSA TEC Assessment that offered the following conclusions:

- No studies directly comparing the outcomes of high dose chemotherapy with allogenic stem cell support with either conventional chemotherapy or high dose chemotherapy with autologous stem cell support have been reported. One retrospective study directly compared the outcomes of allogenic support with those of autologous support. However, this report only provided outcomes that were combined for all myeloma patients, regardless of whether their disease was responsive or refractory to treatment.
- Indirect comparisons suggest that allogenic stem cell support is associated with a 39%−55% 5-year survival, while the comparable figure for autologous stem cell support is 36%−52%.

A review of the literature since 1996 does not provide data to alter the above conclusion. In a 1999 review of the data regarding allogenic stem cell support, Kyle reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40%. In addition, relapse of multiple myeloma is common such that few patients are cured. In 2000, Russell reported overall transplant related mortality of 30% in 25 patients transplanted with allogenic stem cells. Fifteen patients continued in complete remission at median follow-up of 3.4 years. Candidates for allogenic stem cell support tend to be younger than the average age of patients with multiple myeloma and in better overall condition and thus may have a better prognosis no matter what the treatment. Therefore, randomized trials are required to determine whether any possible benefit associated with allogenic stem cell support is truly related to the therapy rather than the underlying patient selection criteria.

High-dose chemotherapy and allogenic stem cell support after a prior failed course of high-dose chemotherapy and autologous stem cell support in the treatment of a variety of malignancies, including multiple myeloma was assessed in a 2000 BCBSA TEC assessment. The BCBSA TEC assessment found that there were inadequate data to permit conclusions about this treatment strategy.

In April 2002 The Cancer Care Ontario Initiative published an evidence-based practice guideline for the role of HDC and stem cell transplantation in the treatment of multiple myeloma. The guidelines make the following recommendations:

3. Autologous transplantation is recommended for patients with stage II or III myeloma and good performance status. Evidence of benefit is strongest for patients who are younger than 55 years of age and have a serum creatinine level less than 150 micromol/L (< 1.7 mg/dL).
4. Allogenic transplantation is not recommended as routine therapy.
5. Patients potentially eligible for transplantation should be referred for assessment early after diagnosis and should not be extensively exposed to alkylating agents before collection of stem cells.
6. Autologous peripheral blood stem cells should be harvested early in the patient's treatment course. The best available data suggest that transplantation is most advantageous when performed as part of initial therapy.
7. The comparative data addressing the specifics of the transplantation process are insufficient to allow definitive recommendations. In the absence of such data, a single transplant with high-dose melphalan, with or without total-body irradiation, is suggested for patients undergoing transplantation outside a clinical trial.
8. At this time, no conclusions can be reached about the role of interferon therapy after transplantation.

Non-Hodgkin's Lymphomas

This policy was initially based on 4 BCBSA TEC assessments, summarized below. It has been updated annually with literature searches to supplement evidence reviewed in the TEC Assessments. The policy is again updated in November 2003 with a literature search for evidence published subsequently. A 1987

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

BCBSA TEC assessment focused on high dose chemotherapy (HDC) and autologous stem cell support for intermediate and high-grade lymphomas. The following conclusions were offered:

> The available evidence suggested that, based on total tumor response rates and complete response rates in patients with intermediate or high-grade lymphomas, the use of HDC with autologous stem cell support produced outcomes comparable to salvage therapy for intermediate and high-grade lymphomas. It should be noted that the data available at that time did not permit assessment of autotransplant outcomes for transformed lymphomas, and thus the policy on transformed lymphomas is based on the 1995 assessment of follicular lymphomas.

A 1990 BCBSA TEC assessment focused on HDC and allogenic stem cell support for intermediate and high-grade lymphomas. The following conclusions were offered:

> The rationale for HDC and allogenic stem cell support in intermediate or high-grade lymphomas was based on the success seen with HDC and autologous stem cell support, where the estimated 3−5-year survival is 40%−60%. However, some patients were not candidates for autologous stem cell support due to chronic marrow hypocellularity or malignancy involving the bone marrow. Allogenic stem cell support provided an alternative.
>
> The data suggested that the 3−5-year survival rates associated with allogenic stem cell support were comparable to those associated with autologous stem-cell support.

A 1995 BCBSA TEC assessment focused on HDC with either autologous or allogenic stem cells support for low and intermediate grade follicular lymphomas. The following conclusions were offered:

> Data were minimal regarding outcomes of allogenic stem cells support, and most reports focused on the outcomes associated with high dose chemotherapy without regard to the source of stem cells. Thus, the Assessment only compared outcomes after HDC supported by any source of stem cells to outcomes after conventional dose regimens. Whether there was a treatment advantage for allogenic or autologous stem-cell support was unknown.
>
> There were inadequate data to determine the treatment effectiveness of high dose therapy with either allogenic or autologous stem cell support for low grade follicular NHL as either primary therapy or as salvage therapy after relapse and transformation to a higher-grade NHL histology.
>
> Sufficient data were reported for HDC as salvage therapy to treat low-grade follicular lymphoma that had failed primary therapy without transformation to a higher grade. In this group of patients, the disease-free survival at 5 years is 10%−66% after HDC and only 2%−21% after conventional-dose alternatives. Given the natural history of this indolent disease, which is one of repeated relapses and progressively shorter durations of remission, improvement in disease-free survival was considered a good predictor of improvement in overall survival. It should be noted that this Assessment did not specifically look at follicular large cell lymphoma, which was categorized as an intermediate grade lymphoma. The conclusions of the 1987 and 1990 TEC assessments thus apply to this unusual subtype of lymphoma.

A review of the literature regarding HDC as a treatment of follicular NHL published since 1995 does not alter the conclusions of the 1995 BCBSA TEC assessment. Specifically, review articles published since its completion conclude that evidence is still insufficient to support routine use of HDC in treating patients with follicular NHL in first remission. Morrison and Peterson state that the available data are limited, follow up is short, and no direct comparisons with conventional treatment have been conducted in controlled trials. They concluded that it is difficult to determine the role of HDC with autologous stem cell support in treating patients in first remission, based on the data available at that time. Blay and Phillip noted that it is unclear whether the reported results comprised improved health outcomes patient selection bias. These authors suggested that comparing outcomes of HDC plus autologous stem-cell support with those of alternatives required prospective, controlled trials.

Updates of earlier articles and new sources of data also confirm the conclusions of the 1995 BCBSA TEC Assessment on use of HDC for patients with relapsed follicular NHL that has not undergone transformation. Evidence was consistent with earlier estimates of overall response, response duration, disease-free survival, overall survival, and treatment-related mortality. The University of Nebraska and Dana Farber have published long-term follow-up data showing median overall survival of 6 years or more. Subsequent data on overall tumor response (range 82%−93%) and median response duration (3.1 years,

over 4 years) continued to show an advantage of HDC over conventional chemotherapy. Five-year disease-free survival was between 19% and 66%, which also was superior to conventional chemotherapy.

In 2000 and 2001, two articles and one abstract provided the only new evidence on the use of HDC for patients with follicular NHL that has undergone transformation. Considerable heterogeneity remained among patients in these series, and outcomes were also quite variable. The published literature did not permit pooling of outcomes by baseline patient characteristics to determine whether outcomes vary predictably. Thus, findings available at that time did not resolve uncertainty on outcomes of HDC plus stem-cell transplants for this indication.

A 2000 BCBSA TEC assessment focused on high dose chemotherapy and allogenic stem cell support after a prior failed course of high dose chemotherapy and autologous stem cell support, in the treatment of a variety of malignancies including non-Hodgkin's lymphoma. The BCBSA TEC assessment found that data were inadequate to permit conclusions on outcomes of this treatment strategy compared to alternatives.

This policy is again updated in November 2003 based on the published literature. The update focuses on indications for HDC plus hematopoietic stem-cell transplants previously considered investigational, including consolidating a first CR, treating follicular NHL that relapsed with transformation; tandem transplants; and allotransplants for patients who have failed a prior autotransplant. In addition, evidence was sought on transplant outcomes for patients with distinct lymphoma subtypes defined by WHO/REAL classification scheme but merged with others in the IWF scheme. Published results relevant to each of these indications are summarized below.

Newly Defined NHL subtypes

Many new NHL subtypes defined by the WHO/REAL classification scheme have not previously been classified as indolent, intermediate or aggressive lymphomas. Data reported by the NHL Classification Project suggest that clinical characteristics, prognostic features, and survival rates for patients with some newly defined entities (e.g., mantle cell and peripheral T-cell lymphomas) may be closer to those intermediate or aggressive NHLs than to the indolent lymphomas. Other new NHL subtypes (e.g., marginal zone B-cell lymphoma of extranodal mucosa-associated lymphoid tissue) are closer in these respects to indolent lymphomas. Limited evidence is available on autotransplant outcomes for homogeneous groups with these newly defined NHL subtypes.

The updated literature search identified 2 studies reporting outcomes of autotransplants for mantle cell lymphoma. A retrospective analysis on 40 patients transplanted between 1991 and 1998 reported that median overall survival was 47 months (65% alive at 2 years) and median event-free survival was 17 months (36% at 2 years). However, only 5 (13%) of these patients were transplanted in a first CR, and outcomes were not reported separately for these patients. A second study reported 68% overall survival and 55% event-free survival at 3 years after treatment. Autotransplants were part of first-line therapy for 9 of the 24 patients included in this study, and only 3 of the 9 were in first CR at the time of transplant. Two of the 3 died with mantle cell lymphoma at 4 and 47 months after transplant, while the third was alive at 24 months' follow-up. A review that summarized data from 8 studies on previously treated patients and 3 studies on patients in first CR concluded that evidence was insufficient to clearly establish a role for autotransplants to consolidate a first CR in patients with mantle cell lymphoma. Note that the review also concluded the available evidence did not demonstrate a clear survival advantage for autotransplants as salvage when compared with conventional-dose salvage.

Two retrospective studies reported autotransplant outcomes for groups with a variety of peripheral T-cell lymphomas. Blystad et al. treated 40 patients with chemosensitive disease, of whom 17 were in a first complete or partial remission and 23 were in a second or third complete or partial remission. With a median 35 months' follow-up, overall survival was 58% at 3 years, event-free survival was 48%, and relapse-free survival was 56%. Rodriguez et al. reported on 36 patients, all with recurrent, relapsed, or refractory disease (i.e., none in a first CR). Overall survival at 3 years was 36% and progression-free survival was 28%. Taken together, these reports are insufficient to determine whether autotransplants improve outcomes for peripheral T-cell lymphoma patients in a first complete remission.

Osteosarcoma

Osteosarcoma most typically arises in the appendicular skeleton of adolescents. The principal treatment is chemotherapy before and/or after surgical excision. The most important prognostic factor is the presence of metastases at the time of diagnosis; these patients can expect only a 20%−30% long-term survival. Tumors arising in the axial skeleton also carry a poor prognosis due to the impossibility of surgical excision.

The most active drugs in osteosarcoma are methotrexate and doxorubicin. However, these drugs are not suitable for high dose regimens; methotrexate is cell cycle specific and the principle toxicity of doxorubicin is cardiac, not hematopoietic. For this reason, high dose chemotherapy has been rarely used for osteosarcoma.

Fagioli and colleagues studied the feasibility of tandem high dose carbolplatin and etoposide followed by stem cell transplant in patients in metastatic relapse of osteosarcoma. Patients responding to the first round of high dose chemotherapy received a second round 4−6 weeks later. The authors reported a high complete response rate. However, responses were not durable. The 3-year overall survival rate was 20% and the 3-year disease free survival rate was 12%.

Ovarian Epithelial Carcinoma

The 1998 BCBSA TEC Assessment did not identify any studies reporting outcomes of allogenic transplants for patients with ovarian cancer. A separate 1999 BCBSA TEC Assessment evaluated the use of high-dose chemotherapy with allogenic stem cell support (HDC/AlloSCS) as a salvage therapy after a failed prior course of HDC/AuSCS. There were no data regarding outcomes of this strategy as therapy for epithelial ovarian cancer.

This policy has been updated annually based on a MEDLINE literature search for articles in English reporting results of hematopoietic stem-cell transplantation for patients with ovarian cancer. In addition, the National Cancer Institute's (NCI's) database of clinical trials (PDQ) was searched for ongoing trials investigating high-dose therapy for patients with ovarian cancer.

The updated literature searches have failed to identify reports from randomized trials directly comparing high-dose and conventional therapies. Several uncontrolled studies were published after the 1998 BCBSA TEC Assessment. These reported retrospective or prospective analyses on outcomes of high-dose regimens followed by AuSCS for ovarian cancer patients who were previously untreated, had residual disease or a responding relapse, or for mixed groups of these patients. Registries in North American and Europe also reported retrospective analyses that may include some of the same patients. Taken together, these data were judged inadequate to alter conclusions of the 1998 BCBSA TEC Assessment or this medical policy. Recent reviews and an editorial did not cite convincing evidence that benefits from high-dose therapy is superior to those of conventional-dose management for any group of patients with ovarian cancer.

The PDQ search identified only 3 open trials specifically focused on patients with ovarian cancer investigating high-dose chemotherapy followed by hematopoietic stem-cell transplant. These included:

- A Phase I/II dose-escalation study investigating increasing doses of topotecan, combined with a fixed dose of etoposide, followed by autologous peripheral blood stem cells for patients with persistent or recurrent ovarian cancer (NCI-G97-1327);
- A Phase II trial using cyclophosphamide, carboplatin, and mitoxantrone followed by autologous bone marrow transplant for patients with refractory or relapsed ovarian cancer (NCI-V91-0058);
- A Phase III trial randomizing patients with optimally debulked stage III or IV ovarian cancer not previously exposed to chemotherapy to sequential high-dose therapy with paclitaxel/cyclophosphamide plus G-CSF, then paclitaxel/carboplatin plus G-CSF, followed by autologous peripheral blood stem cell support, or to conventional-dose management with carboplatin/paclitaxel (EU-99040).

Note that the randomized trial is being conducted in Europe and only uncontrolled studies are open in the U.S. Note also, that other trials are open for patients with advanced ovarian cancer, but are enrolling patients with various other solid tumors as well. These uncontrolled studies are investigating use of allogenic stem cells (after non-myeloablative regimens) or autologous stem cells combined with immunotherapy or gene therapy.

Primary Amyloidosis

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

Treatment for amyloidosis targets the aberrant plasma cell clone to prevent further synthesis and deposition of the amyloid protein. Chemotherapeutic drug combinations such as melphalan plus prednisone (MP) or vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD), well-established regimens for myeloma, are among the conventional therapies for patients with primary amyloidosis. However, as is true for myeloma, these regimens rarely cure patients. Approximately 30% of amyloidosis patients respond to MP and median survival ranges from 1−2 years. VAD therapy is usually limited to patients without peripheral neuropathy or cardiomyopathy, both common complications of amyloidosis. Since results of standard therapies for primary amyloidosis are unsatisfactory, clinical studies were begun on high-dose chemotherapy with autologous stem cell support (HDC AuSCS). Data showing HDC AuSCS improved outcomes for those with myeloma provided an additional rationale for studies on patients with amyloidosis.

Several case series have examined the outcomes of HDC AuSCS in patients with primary amyloidosis. In one of the first published reports, Comenzo and colleagues reported on 25 patients. With a median follow-up, 68% were alive, and 11 of these 17 patients had experienced improvement in amyloid related organ involvement. Three patients experienced relapses at 12 and 24 months. Gertz and colleagues reported on a case series of 20 patients; 13 were alive at follow-up of 3−26 months. Of these, 12 had a hematologic or organ response. Five of the 6 patients with cardiac involvement died post-transplant. The authors concluded that HDC AuSCS for primary amyloidosis had a higher morbidity and mortality compared to multiple myeloma. The best results were seen in those patients with nephrotic syndrome as their only manifestation. Moreau and colleagues retrospectively examined the morbidity and mortality of HDC AuSCS in 21 cases of primary amyloidosis and reported that the major prognostic factor for both response and survival was the number of clinical manifestations at the time of the transplant. For example, among patients with 2 or more manifestations, the overall and event-free survival were 11.1% compared to 91.7% and 46.3%, respectively, in patients with only one clinical manifestation of disease. Saba and colleagues reported that among 9 patients with primary amyloidosis and predominant cardiac involvement, only 3 patients recovered and left the hospital. One of these patients died within 6 weeks of discharge. The authors concluded that HDC AuSCS should be used with great caution in patients with cardiac involvement. Comenzo suggested that heart transplant in conjunction with HDC AuSCS may be required to improve the outcomes of patients with cardiac involvement. R.L. Comenzo, M.D., recently reviewed published reports on results of HDC AuSCS for amyloidosis. A total of 133 amyloidosis patients were included in this summary of 5 case reports and 6 uncontrolled series. Eighty-five patients (64%) survived at least 1 year after HDC AuSCS. Symptoms from organ deposition of amyloid protein reportedly improved in 55 patients (65% of survivors). Amyloid scans documented resorption of protein deposits in the affected organs of many of those who improved. However, 34 patients (26%) died in the peritransplant period. Causes of treatment-related mortality included cardiac complications, gastrointestinal bleeding, sepsis, visceral rupture, and multiorgan failure. Many of the peritransplant deaths were attributed to extensive and irreversible organ damage prior to HDC AuSCS. Subsequently, most investigators carefully selected amyloidosis patients for transplant. Based on the accumulated experience, the authors recommended HDC AuSCS for the following patients with primary amyloidosis:

- Patients less than 60 years old; AND
- Have 2 or fewer organ systems involved with amyloid protein; AND
- Are free of symptomatic cardiac involvement.

While the above case series suggest that HDC AuSCS may have a beneficial effect, only a comparative trial can confirm that the treatment effect is real and not primarily related to patient selection alone. As with many applications of HDC AuSCS, only patients with primary amyloidosis in overall good condition may be considered candidates for high-dose therapy. These patients are likely to have better outcomes with any treatment, including standard therapy, compared to the overall population of patients with primary amyloidosis. This issue was addressed by Dispenzieri and colleagues who retrospectively examined the outcomes of patients with primary amyloidosis treated with conventional therapy who would have been considered candidates for HDC AuSCS. Their criteria for HDC AuSCS candidacy included age less than 70 years, cardiac interventricular septal thickness less than 15, cardiac ejection fraction more than 55%, serum creatinine less than 2 mg/dl, and direct bilirubin less than 2.0 mg/dl. The authors reported that these hypothetical candidates for HDC AuSCS had a median survival with conventional therapy of 42 months, compared to a median survival of only 18 months among all patients with primary amyloidosis. The authors concluded that a randomized trial is needed to assess the true effect of HDC

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

AuSCS. Comenzo and Gertz identified 2 key predictors of survival among a subset of patients with amyloidosis to be serum creatinine level at time of high dose chemotherapy and the number of visceral organs involved. The 30-month actuarial survival is 72% in patients whose serum creatinine is less than 1.5 mg/dL and who have two or fewer organs involved with amyloid deposits. The authors found that the presence of cardiac amyloid contribute significantly to transplant-related mortality.

Primitive Neuroectodermal Tumors (PNET)/Neuroblastomas

Initial therapy of PNETs focuses on neurosurgical resection and radiation therapy with or without adjuvant conventional chemotherapy; 60% of children survive 5 years or more with this approach. In patients with residual tumor or recurrent disease, further surgery or radiation therapy is usually not an option, and conventional chemotherapy is rarely successful. Therefore, high dose chemotherapy for CNS PNET has focused primarily on recurrent disease. The most common CNS PNET is medulloblastoma, and thus most of the data focus on this diagnosis.

This policy was initially based on a literature search for studies published through 1999. No comparative trials were found. The largest case series included 23 patients with recurrent medulloblastomas treated with high dose carboplatin, thiotepa, and etoposide. Seven were event-free survivors at a median of 54 months, with overall survival estimated at 46% at 36 months. In contrast the median survival after recurrent medulloblastoma treated with conventional therapy may be as low as 5 months. High dose chemotherapy is expected to be most effective when the disease burden is minimal. Thus, Dunkel and colleagues suggested increased surveillance for recurrence, or aggressive surgical debulking at the time of recurrence. The authors also acknowledge the potential for effects of patient selection bias on their results, since not all patients eligible for the protocol were enrolled.

Other CNS PNETs are uncommon and include pineoblastoma, ependymoblastoma, and central neuroblastoma. There are few data regarding high-dose therapy for these rare tumors, although it was thought that the results with medulloblastoma might be extrapolated to other PNETs.

In 2001 Strother and colleagues published data from a study including 53 patients with newly diagnosed medulloblastoma or supratentorial PNETs/ of whom had high-risk disease and 34 had average-risk disease. After surgery and radiotherapy, the study used 4 cycles of HDC with cyclophosphamide, cisplatin, and vincristine, followed by autologous stem-cell support. Patients with high-risk disease also received topotecan between surgery and radiotherapy. Early actuarial analysis of outcomes yielded estimates of 94% progression-free survival at 2 years for average-risk patients and 74% for high-risk patients. In 4/2002, Bertuzzi and colleagues published results of a study in which fourteen patients with poor prognosis PNETs were treated with high dose chemotherapy followed by autologous stem cell transplant. The overall response rate for the PNET patients was 86% (72% CR, 14% PR). Their overall two-year survival was 50%.

Other PNETs are uncommon and include pineal blastoma, ependymoblastoma, and central neuroblastoma. There are very little data regarding high dose therapy for these rare tumors, although it is thought that the results with medulloblastoma may be extrapolated to other PNETs.

A November 2003 search of the National Cancer Institute (NCI) database on ongoing clinical trials identified three open phase II trials of HDC plus autologous stem cell support that specifically focused on medulloblastoma or other CNS PNETs. The first uses intensive cisplatin, vincristine, cyclophosphamide and etoposide with or without methotrexate followed by radiation therapy for patients with newly diagnosed high-stage medulloblastoma, PNETs or incompletely resected ependymoma. The second uses dose intensive thiotepa and carboplatin for recurrent medulloblastoma or PNETs, and the third uses craniospinal irradiation followed by high dose vincristine, cisplatin, cyclophosphamide, and amifostine for newly diagnosed medulloblastoma or other PNETs. The search did not identify any phase III trials for these patients.

Retinoblastoma

Retinoblastoma is the most frequent ocular tumor in children, with unilateral cases in 62.5% of patients. While most cases appear to arise spontaneously, a significant fraction is hereditary. Retinoblastoma may be cured with surgery, radiation, and/or chemotherapy. However, central nervous system involvement or extraocular dissemination is associated with a grave prognosis.

A 2002 search of the literature reveals one published study of four patients with metastatic retinoblastoma that did not involve the central nervous system. Patients were treated with high dose carboplatin, thiotepa and etoposide followed by autologous stem cell infusion. Sites that had bulky disease were irradiated following recovery from high dose chemotherapy. At 46−80 months follow-up all patients were alive. This single study is too small to be able to reach conclusions concerning the effectiveness.

Rhabdomyosarcoma

Rhabdomyosarcoma, arising from a primitive myocyte, is the most common malignant tumor of the soft tissues in children. The most common primary site is the orbit. Treatment may include surgery, irradiation, and/or chemotherapy. While rhabdomyosarcoma is considered chemosensitive, high-risk tumors are those presenting with metastases or tumors that relapse after initial standard therapy.

Similar to other pediatric solid tumors, high-dose chemotherapy has been studied as salvage therapy for patients with recurrent or refractory tumors, or as initial therapy in patients with high-risk tumors. Due in part to its rarity, data is relatively scarce. The European Bone Marrow Transplant Solid Tumor Registry has reported that the median survival after high dose chemotherapy in patients with relapsed or progressive disease is only 8 months. These disappointing results have focused research on high dose chemotherapy as consolidation therapy in patients with high-risk tumors. The European Bone Marrow Transplant Solid Tumor Registry reported on 62 patients who received after high dose chemotherapy in either first complete or partial response. Overall, the 5-year survival rate was 22%. The survival rate of the 40 treated during a complete remission was 34%, but 0% for those treated during a partial remission. In a summary of the data, Chen and Civin conclude that the data do not support that high dose chemotherapy as a consolidation strategy is associated with an improved outcome compared to conventional chemotherapy. In a non-randomized study, Carli et al. compared results in 52 children with rhabdomyosarcoma who received high dose chemotherapy to children who received standard chemotherapy. Patients in both groups were in complete remission after 6 courses of induction chemotherapy. The addition of high dose chemotherapy and stem cell transplant did improve overall survival compared to standard chemotherapy.

In November 2002 Hawkins and colleagues reported results of a series of 23 children with metastatic sarcomas, primarily rhabdomyosarcoma (n = 6) or Ewing's sarcoma who were treated with a dose intensification schedule. This high dose regimen called for eight rounds of multiple chemotherapy drugs followed by stem cell transplant and administration of the hematopoietic growth factor, G-CSF. The rounds were administered 21 days apart or following hematopoietic recovery. Following round 6 patients were treated with surgical resection of the tumor. Twelve patients achieved a complete response after chemotherapy alone. Additional 5 patients achieved a complete response after undergoing surgical resection following chemotherapy. One patient died of acute respiratory distress syndrome and 15 patients experienced progressive disease. The 2- and 3-year event free survival rates were 39% and 30% respectively.

Sickle Cell Anemia

Sickle cell anemia accounts for 60%−70% of sickle cell disease in the United States, affecting one out of 600 African Americans. The disease can also occur in people whose ancestors originate from the Mediterranean basin, Arabian Peninsula, the Caribbean, and Central and South America, resulting in more than 50,000 affected persons in the U.S.

The sickle cell mutation is responsible for increased rigidity and adherence of red blood cells, leading to the hallmark features of chronic hemolytic anemia and both acute and chronic hemolytic anemia and tissue injury. Homozygous sickle cell disease can present a varied clinical course from severe and rapid progression to end-stage disease of the brain, kidneys, and lungs to an asymptomatic course or relative states of well-being with periodic crises.

Vaso-occlusive crisis, the hallmark of the disease, is the most common form of acute morbidity and the most frequent cause for hospital admission among sickle cell disease patients. The clinical presentation varies from mild to excruciating pain, with fever and leukocytosis, and may simulate a life-threatening event or progress to one. The frequency of occurrence can vary from daily to yearly; the average rate is reported as 0.8 episodes per patient-year.

Other than human stem cell transplantation, 2 therapeutic approaches offer evidence of ameliorating many of the hemolytic and vaso-occlusive manifestations associated with homozygous sickle cell

disease. Chronic transfusion is considered standard treatment of severe complications of sickle cell disease. A newer approach, hydroxyurea administration, has been the subject of clinical trials. While it has been shown to reduce the frequency of painful crises, no effect on stroke recurrence has been demonstrated. Chronic transfusion and hydroxyurea are both palliative, while allogenic stem cell transplant represents the only potentially curative therapy.

This policy is based in part on a 1996 TEC Assessment, which found that the scientific evidence indicates disease-free survival rates following allogenic bone marrow transplant range from 73%–100% with follow-up periods of a median of 16 months to 37 months. In a recent clinical study, Walters et al. followed 26 children a median 57.9 months following allogenic stem cell transplant who had a survival rate of 94%, and an event-free survival of 84%. Twenty-two of the 26 children experienced complete resolution of complications of sickle cell disease, and none experienced further pain episodes, stroke, or acute chest syndrome. The authors concluded that these data confirm that allogenic HSCT establishes normal erythropoiesis and is associated with improved growth and stable CNS imaging and pulmonary function in most patients. To date, all reported cases of human stem cell transplantation in sickle cell anemia have used HLA-matched, related donors. There are no data available concerning allogenic human stem cell transplantation from unrelated or mismatched donors.

A December 2003 MEDLINE search of the literature revealed no new clinical studies on high dose chemotherapy followed by hematopoietic stem cell support for the treatment of genetic diseases or acquired anemias.

Solid Organ Malignancy

This policy is based in part on a 1995 BCBSA TEC assessment that focused on the malignancies listed above in the policy/criteria section. The assessment offered the following conclusions:

While 125 articles were identified that reported on the results of HDC in a variety of solid tumors, only 17 included survival data from groups of patients with the same cancer. These studies reported on 4 indications: advanced small cell lung cancer, advanced colorectal cancer, malignant melanomas, and inoperable gastric cancer. The evidence did not permit conclusions as to the effect of HDC on patient survival.

Review of the literature since the 1995 BCBSA TEC assessment does not change its conclusions. In fact, in the intervening years, there has been declining enthusiasm for HDC for solid tumors, particularly those such as gastrointestinal malignancies or malignant melanoma, which are generally considered to be chemoresistant. As an example, Seynaeve and Verweij reviewed the literature regarding high dose chemotherapy for adult sarcomas. The authors point out that these tumors are generally chemoresistant and that higher doses have not been shown to overcome this resistance. Therefore, research efforts should focus on identifying new active drugs. In contrast, small cell lung cancer is considered chemosensitive, and therefore, there has been ongoing interest in high dose chemotherapy. Dana Farber Cancer Institute and Beth Israel Hospital have reported the most extensive experience, consisting of 50 patients with limited stage disease and 25 patients with extensive disease. Of the highly selected patients who achieve a complete or near complete remission prior to high dose therapy, the 5-year event-free survival was 52%. Of the extensive disease patients, 15%–20% remained progression free more than 2 years after high dose therapy. Without a control group, patient selection bias cannot be evaluated.

A January 2002 search of the literature revealed six new phase I/II clinical trials previously not reviewed which evaluate the feasibility of HDC in adult patients with small cell lung cancer, non-small cell lung cancer, advanced soft tissue sarcoma, Ewing's sarcoma and transitional cell urothelial carcinoma. Each trial treated small numbers of patients. Two of the series report survival rates: 24% for Ewing's sarcoma and 23% in advanced soft tissue sarcoma. Toxicity was significant and the studies failed to show that HDC with stem cell support improves the probability of event free or overall survival.

A 1999 BCBSA TEC assessment evaluated the use of high dose chemotherapy with allogenic stem cell support as a salvage therapy after a failed prior course of high dose chemotherapy with autologous stem cell support for solid tumors. There were inadequate data to permit conclusions.

A review by Nieto and Shpall and a report from the European Group for Bone Marrow Transplantation's Solid Tumors Working Party agreed that evidence was still insufficient to establish a definite role for HDC and autologous transplantation in small-cell lung cancer. Nieto and Shpall also concluded that evidence was inadequate to demonstrate a survival benefit from HDC for melanoma or sarcoma. Other

malignancies listed in the "policy/criteria" section of this document were not considered in either of these reviews. Similarly, a 2001 clinical guideline on HDC with bone marrow or stem cell support, issued by the National Comprehensive Cancer Network, did not include any malignancy listed in the policy document among those with even the lowest level (limited, albeit promising) of supportive evidence.

A December 2003 updated search of the literature revealed no new published clinical studies of high dose chemotherapy followed by hematopoietic stem cell support for the treatment of the solid tumors in adults addressed in this policy.

Tandem Transplants

The updated literature search identified 2 uncontrolled pilot studies on outcomes of tandem transplants as part of initial therapy for patients with aggressive non-Hodgkin's lymphoma. One study (n = 36) was limited to patients at high- or high-intermediate risk for relapse after achieving a first CR. The second (n = 25) included 11 patients with low-intermediate risk and 14 patients at higher risk. Note also that only 17 of the 25 patients in the second study were given full courses of induction therapy, and only 8 of these achieved a CR. Thus, patient populations in these studies differed with respect to disease status at transplant. Neither study included a control group of similar patients managed with a single transplant. Therefore, results reported by these studies did not provide convincing evidence that tandem transplants improved outcomes when compared with single transplants for patients with NHL. A recent review also concluded that available data were insufficient to determine whether outcomes of tandem transplants were superior to outcomes of single transplants for patients with NHL.

The updated literature search found no prospective controlled studies comparing allotransplants to alternative strategies for managing failure (progression or relapse) after an autotransplant for NHL. Only 2 reports that included patients with NHL have been published since the 2000 TEC Assessment on this topic. One series included 4 NHL patients who relapsed after an autotransplant, while the second included 2 patients with mantle cell lymphoma that had relapsed after an autotransplant reportedly respond to conventional-dose treatment and achieve long-term survival.

The paucity of outcomes data for allotransplants after a failed autotransplant is not surprising. Patients are rarely considered eligible for this option either because their relapsed lymphoma progresses too rapidly, because their advanced physiologic age or poor health status increases the likelihood of adverse outcomes (e.g., from GVHD), or because they lack a well-matched donor. A few institutions have treated up to 15 or 20 such lymphoma patients (NHL plus Hodgkin's disease) in the last 10−20 years Thus it appears highly unlikely that adequately powered, randomized trials comparing this therapy to alternatives could ever be conducted, even by a multi-institutional group. Nevertheless, several institutions report that a minority of patients achieved long-term disease-free survival following an allotransplant for relapsed NHL after an autotransplant. Factors that apparently increase the likelihood of survival included a chemosensitive relapse, younger age, and a long disease-free interval since the prior autotransplant, availability of an HLA-identical sibling donor, and fewer chemotherapy regimens prior to the failed autotransplant. Thus, clinical judgment, confirmed by external review, can play an important role to select patients for this treatment with a reasonable likelihood that potential benefits may exceed harms.

An October 2009 literature review for multiple myeloma (MM) found protocols for Total Therapy 1, 2, and 3. These protocols use intensive chemotherapy (6−8 medications) followed by autologous tandem transplant. Total Therapy 1, 2, and 3 are designed for newly diagnosed patients. This therapy has not been tested in multi-centered randomized clinical trials. Kumar et al. did not prove that tandem auto transplants were any better than the single auto transplants when performed during remission after a successful induction therapy. This was a meta-analysis of 6 prospective randomized clinical trials, and 1,800 patients. Kumarj et al. concluded that even as a first line treatment, tandem auto transplants do not offer results that are statistically better that the single auto transplant.

Recent studies have supported tandem transplant to improve health outcomes in patients defined as having high risk for post-operative recurrence of the disease using the Neuroblastoma Risk Group Staging system (NRGSS) classification system. A Children's Oncology Group study published by Park, et al., in 2016 of 652 eligible patients with HR-NB were randomized to receive single ASCT versus tandem transplant. 3-year EFS and OS were assessed for each group. The aggregate survival for the tandem transplants receiving postablative consolidative immunotherapy was 73.7% compared to 55.4% with a p-value of 0.0009.

Transformed follicular NHL

The literature search update found no randomized trials comparing auto transplants to alternative therapies for patients with follicular or other indolent NHL that has relapsed with transformation to a higher grade. Retrospective series reviewed in the 1995 TEC Assessment and in the 2000 Policy update reported transplant outcomes were particularly poor for patients with follicular NHL that relapsed with transformation. More recent retrospective data are available from a single institution series and a registry analysis. Although these studies lack controls treated with conventional-dose regimens, they directly compare outcomes of autotransplants for transformed NHL to outcomes of autotransplants for relapsed de novo intermediate or aggressive NHL.

The single-institution series reported similar event-free (38% for 18 transformed patients vs. 37% for 100 de novo patients) and overall survival at 4 years (61% vs. 53%, p not significant) for the 2 groups. Transplant-related mortality occurred in only 1 of 18 patients with transformed lymphoma. The registry analysis included 50 patients transplanted for follicular lymphoma that relapsed with transformation/0 matched patients transplanted for follicular lymphoma that relapsed without transformation, and another 200 matched patients transplanted for de novo intermediate or aggressive lymphoma that relapsed. Kaplan-Meier analyses showed no statistically significant differences in overall survival between the group transplanted for transformed NHL and either of the 2 matched comparison groups ($p = 0.939$ versus non-transformed low-grade lymphoma; and $p = 0.438$ versus de novo intermediate/aggressive lymphoma). Similar results were reported in single-institution retrospective series that lacked comparison groups. Taken together, the new results indicate that autotransplants improve outcomes for patients with relapsed NHL whether it is de novo intermediate or aggressive disease or indolent disease that has relapsed with or without transformation.

Wilms' Tumor

Wilms' tumor is the most common primary malignant renal tumor of childhood and is typically treated with a combination of surgery, radiation therapy, and chemotherapy. Complete cures are possible with conventional therapy even for relapsing tumors or those tumors presenting with metastatic disease. However, high risk disease can be identified principally based on the histologic components of the tumor, but also including those tumors that relapse within 6 months of initial treatment, involvement of sites other than the lungs or abdomen, or an abdominal recurrence after irradiation.

There is limited information regarding high dose therapy for Wilms' tumors. In 1 study, a total of 29 patients with relapsed and heavily pretreated Wilms' tumors were treated with high dose chemotherapy. A total of 28 patients achieved a complete remission, with 14 patients remaining in complete remission for a median of 19 months. Because of the success of conventional chemotherapy, few patients have been treated with high dose chemotherapy as consolidation of a first complete remission.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Code range for transplant preparation of hematopoietic progenitor cells
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Bone marrow or blood-derived peripheral stem cell transplantation, allogenic
38241	Bone marrow or blood-derived peripheral stem cell transplantation, autologous
38242	Allogenic donor lymphocyte infusion

Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

86812	HLA typing; A, B, or C (eg, A10, B7, B27), single antigen
86813	HLA typing; A, B, or C, multiple antigens
86816	HLA typing; DR/DQ, single antigen
86817	HLA typing; DR/DQ, multiple antigens
86821	HLA typing; lymphocyte culture, mixed (MLC)
86825	Human leukocyte antigen (HLA) crossmatch, non-cytotoxic (eg, using flow cytometry); first serum sample or dilution
86826	Human leukocyte antigen (HLA) crossmatch, non-cytotoxic (eg, using flow cytometry); each additional serum sample or sample dilution (List separately in addition to primary procedure)
96401-96450	Chemotherapy administration code range

HCPCS CODES

J9000-J9999	Chemotherapy drugs code range
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition

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Human Stem Cell Transplantation (HSCT), Bone Marrow Transplantation (BMT), continued

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For Solid Organ Malignancies

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MEDICAL POLICY

MRI FOR PROSTATE CANCER RADIATION TREATMENT PLANNING

Policy # 486
Implementation Date:9/13/11
Review Dates: 8/16/12, 8/15/13, 8/28/14, 8/20/15, 8/25/16, 8/17/17, 9/20/18, 8/8/19, 8/20/20, 8/19/21, 7/27/22, 8/23/23, 8/21/24
Revision Dates:

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Prostate cancer is the most frequent non-dermatologic cancer among U.S. males. A man's lifetime risk of prostate cancer is 1 in 6. Prostate cancer is the second leading cause of cancer death in men, exceeded only by lung cancer. If diagnosed with prostate cancer, men have multiple treatment options to consider depending upon the stage at diagnosis, and the associated cancer characteristics. These treatment options can include surgical removal of the gland, external beam radiation therapy, low-dose radiation seed implants into the prostate gland, proton beam therapy, cryotherapy, or high-dose radiation brachytherapy. All therapies have similar efficacy and side effects, with none demonstrating superiority, except for select cases, thus, the choice of therapy is often based upon the patient's preference.

As it relates to radiation therapy in the treatment of prostate cancer, magnetic resonance imaging (MRI) is a new tool being promoted for treatment planning in patients with prostate cancer. In treatment planning for radiation treatment, the process of designing a radiation field starts with simulation, which is used to map out the extent of disease and its relationship to other organs when the patient is in the treatment position. Once simulation has been performed, the treatment position cannot be altered without the risk of inaccurate treatment delivery. Fluoroscopy was used to outline the boundaries of the field, with plain film x-rays being taken to include the general outline of the area to be treated. Although fluoroscopic simulators still are in use, many three-dimensional (3D) treatment planning systems now are available to permit more accurate or more conformal delivery of radiation treatment. 3D treatment planning systems use CT data (in some cases, augmented by fusion with other radiologic modalities) to simulate radiation delivery. This can be accomplished in a variety of ways:

CT images can be transferred to a computer-based treatment planning system. The fields are designed using the CT-based planning system, with verification (i.e., checking the treatment position) performed by taking x-ray films on a conventional simulator.

The most efficient method is to use a CT simulator to set up the radiation fields. The CT simulator combines the processes of obtaining CT images and field design. CT images of the patient are transferred directly to a computer system that allows the physician to outline the tumor volume and critical structures on individual CT slices. This, in effect, produces an accurate -D recreation of both the tumor that is to be treated and normal tissues that are to be avoided during the delivery of radiation.

Additional data from magnetic resonance imaging (MRI) scanning or positron emission tomographic imaging can be fused with images obtained in the CT simulator in order to improve the accuracy of planning.

Prostate MRI exams involve the use of an endorectal coil, a thin wire covered with a balloon, placed inside the rectum. This coil helps focus on the prostate and surrounding structures; it also enables the radiologist to perform magnetic resonance (MR) spectroscopy, which can provide additional information on the chemical makeup of cells present in the prostate gland. Coils placed either inside the rectum or

underneath the patient's lower back (i.e., a body coil) detect the MR signal released from the patient and will subsequently send this data to a computer. Currently, no data or studies have demonstrated superior outcomes for radiation therapy using MRI scans in planning the treatment.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover prostate magnetic resonance imaging (MRI) for radiation treatment planning for prostate cancer. Current evidence has failed to demonstrate superior outcomes for use of prostate MRI compared to alternative procedures.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

A June 2011 Medical Technology report identified 4 systematic reviews and 8 primary literature articles concerning prostate MRI in treatment planning. Currently, the standards for prostate imaging are TRUS and CT. There is no published evidence comparing the role of TRUS vs. CT or TRUS vs MRI in treatment planning for prostate cancer.

In 2009, Hayes published a brief review on 3.0 Tesla MRI for prostate cancer. The group stated: "Improved image quality with 3T MRI may enable adequate imaging of the prostate using external coils rather than endorectal coils that are inserted in the rectum. However, the higher field strength of 3T MRI can cause image distortion, artifacts, and other types of noise … 7 controlled or comparative studies … evaluated 1.5T versus 3T MRI for patients with known or suspected prostate cancer. Results of these studies suggest that, for staging of prostate cancer, external coil 3T MRI has the same diagnostic accuracy as endorectal 1.5T MRI." Hayes concluded that: "Further studies are needed to determine the clinical role of 3T versus 1.5T MRI for the monitoring and staging of prostate cancer."

The Canadian Agency for Drugs and Technologies in Health (CADTH) published an article in 2011 concerning the clinical effectiveness of 1.5T vs. 3.0T MRI. The group cited a 2005 study by Beyersdorff et al., where 24 men with biopsy-confirmed prostate cancer were referred for preoperative staging before radical prostatectomy. All men underwent 3.0T MRI scanning with a torso coil and 1.5T MRI scanning with an endorectal coil, with 17 of the 24 men receiving their scans on the same day. Two radiologists independently viewed the images. Blinding was not possible because of visualization of the different coils. Preoperatively, both technologies showed 73% accuracy for local staging. However, a review of images post-surgery showed that the use of 1.5T MRI displayed statistically significantly better tumor delineation. CADTH also cited a 2006 study by Torricelli et al. who assessed 29 men with biopsy proven prostate cancer who needed staging before radical prostatectomy. The results showed no statistical differences between 1.5 T MRI and 3.0 T MRI in sensitivity and specificity.

The National Institute for Health and Clinical Excellence (NICE) published their guidelines for prostate cancer diagnosis and treatment in 2008. As part of this guideline, it is advised that men with high-risk localized and locally advanced prostate cancer, who are being considered for radical treatment, should have pelvic imaging with either magnetic resonance imaging (MRI) or CT if MRI is contraindicated. The

MRI for Prostate Cancer Radiation Treatment Planning, continued

group also noted that magnetic resonance spectroscopy is not recommended for men with prostate cancer except in the context of a clinical trial.

Of the 8 primary literature articles, 7 involve large patient populations and are generally concerned with MRI's use of prostate cancer staging, the efficaciousness of endorectal-MRI and comparing MRI to CT in treatment planning.

In 2011, Brajtbord et al. found that endorectal-MRI has limited clinical value in preoperatively detecting extracapsular extension and seminal vesicle invasion. Colleselli et al. (2011) also found no tumor could be demonstrated; 13% of patients tested with endorectal-MRI. Only 48.3% of patients were staged correctly, 23.3% were over-staged, and 28.3% were under-staged. The group concluded that the reliability of endorectal-MRI depends on clinical parameters. Higher Gleason scores, unifocal tumors, and smaller prostate volumes ameliorate endorectal-MRI's performance.

Perhaps the most thorough review of MRI's use in prostate cancer treatment planning was published by Jonsson et al. (2010). MR and CT data were collected retrospectively for 40 patients with prostate, lung, head and neck, or brain cancers. They concluded that with respect to treatment planning, MRI can replace CT in all steps of the treatment workflow, reducing the radiation exposure to the patient, removing any systematic registration errors that may occur when combining MR and CT and decreasing time and cost for the extra CT investigation.

In summary, current evidence regarding use of MRI in treatment planning is conflicted and has not clearly established the use of this technology to be superior to either TRUS or CT scanning. No studies have been performed to identify whether use of MRI in treatment planning improves the health outcomes of patients or is more cost-effective.

Billing/Coding Information

Not covered: Investigational/Experimental/Unproven for this indication

CPT CODES

72195	Magnetic resonance (e.g., proton) imaging, pelvis; without contrast material(s)
72196	; with contrast material(s)
72197	; without contrast material(s), followed by contrast material(s) and further sequences

HCPCS CODES

No specific codes identified

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Disclaimer
This document is for informational purposes only and should not be relied on in the diagnosis and care of individual patients. Medical and Coding/Reimbursement policies do not constitute medical advice, plan preauthorization, certification, an explanation of benefits, or a contract. Members should consult with appropriate healthcare providers to obtain needed medical advice, care, and treatment. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the member's individual benefit plan that is in effect at the time services are rendered.

The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Select Health

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MEDICAL POLICY

NON-MYELOABLATIVE HUMAN STEM CELL TRANSPLANTS (BMT OR HSCT) OR "MINI-TRANSPLANTS"

Policy # 216
Implementation Date: 1/26/04
Review Dates: 1/13/05, 1/26/06, 1/26/07, 2/21/08, 2/26/09, 2/18/10, 2/17/11, 2/16/12, 4/15/13, 2/20/14, 3/19/15, 2/11/16, 2/16/17, 2/15/18, 2/20/19, 2/17/20, 2/18/21, 8/20/22, 2/16/23
Revision Dates: 8/26/22

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Advantage (Medicare/CMS), and Select Health Community Care (Medicaid/CHIP) plans. Refer to the "Policy" section for more information.

Description

Allogenic transplantation of stem cells in conjunction with myeloablative (bone marrow killing) chemotherapy is an established therapy for a variety of malignancies, including acute and chronic leukemias and non-Hodgkin's lymphomas. However, pilot studies have shown that donor allogenic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft vs. host tolerance. This manifests as a stable mixture of donor and host blood cells in the bone marrow. Once this stable mixture has occurred (hematopoietic chimerism), further infusion of donor blood cells is done to cause a graft vs. tumor reaction. Non-myeloablative allogenic transplants, also referred to as "mini-transplants" or "transplant lite," are thought to be potentially as effective as conventional myeloablative allogenic transplants but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen.

COMMERCIAL PLAN POLICY/CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers *allogenic* non-myeloablative bone marrow transplants ("mini-transplants") when either A or B are met:

A. Procedure is recommended, endorsed, and performed by Intermountain Transplant Services; **OR**

B. **For all other clinicians, Select Health covers these procedures for myeloablative bone marrow transplants** when the following conditions are met:

All the following conditions must be met for coverage of *allogenic* "mini-transplants":

1. The condition for which the procedure is being requested is currently a covered condition for an allogenic myeloablative bone marrow transplant (full or standard bone marrow transplant).
2. The patient would otherwise qualify for a full bone marrow transplant except for the patient's age or co-morbidities.
3. All other therapeutic options have been attempted or are not considered an option due to proven excessive morbidity/mortality.

Select Health

Non-Myeloablative Human Stem Cell Transplants (BMT or HSCT) or "Mini-Transplants, continued

Limitations/exclusions regarding travel, meal expenses, computerized donor searches, or reimbursement of the bone marrow itself when the live donor or next of kin (in the case of cadaveric donors) sells the marrow are the same as that for full myeloablative transplants.

Conditions for coverage:

- Severe aplastic anemia refractory to other medical treatments
- Acute leukemias (AML, ALL, or AUL)
- Chronic myelogenous leukemia (CML, including subtypes)
- Glioblastoma (in pediatric population only)
- Hodgkin's lymphoma
- Hereditary immunodeficiency disease (including severe combined immunodeficiency disease)
- Multiple myeloma
- Neuroblastoma
- Osteopetrosis
- Thalassemia major
- Chronic lymphocytic leukemia (CLL)
- Myelodysplastic syndrome
- Germ cell cancer

All other conditions not listed above are not covered.

Select Health does NOT cover *autologous* non-myeloablative bone marrow transplants ("mini-transplants") for any condition.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

This assessment is based on a 2001 TEC Assessment that focused on nonmyeloablative stem cell transplant in patients who would not be considered candidates for conventional allogeneic stem cell transplant due to comorbidities. The assessment further focused on those malignancies for which conventional allogeneic stem cell transplant has a proven treatment benefit (i.e., acute and chronic myeloid leukemia, acute lymphoblastic leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma) and those malignancies where the treatment effectiveness of conventional allogeneic stem cell transplant is still uncertain (multiple myeloma, chronic lymphocytic leukemia, myelodysplastic syndrome, malignancies, or solid organs). The TEC assessment did not focus on those patients who would otherwise be considered for a conventional myeloablative transplant. The rationale behind this assessment focus was

Select Health

Non-Myeloablative Human Stem Cell Transplants (BMT or HSCT) or "Mini-Transplants, continued

that, in the literature, it is not possible to clearly distinguish between what would be considered a myeloablative versus a nonmyeloablative conditioning regimen. Therefore, for patients who are considered candidates for a conventional allogeneic transplant, the intensity of the conditioning regimen is primarily one of physician preference. However, for patients who are not considered candidates for a conventional myeloablative transplant, nonmyeloablative transplants represent a unique approach. The following observations and conclusions regarding this latter group of patients were reported:

CML, AML, ALL, HD, NHL ineligible for conventional allogeneic stem cell transplant

- The available evidence was insufficient to permit scientific conclusions. For each of the above malignancies, the sample size was inadequate even when data were pooled from all studies. In addition, the follow-up duration in all the studies ranged from 3 months to slightly more than 1 year. This duration is short, relative to either the natural history of these malignancies or the reported duration of survival after alternative therapies. No data were reported on results of conventional management of well-matched controls; thus, direct comparison of outcomes was not possible.
- The limited evidence suggested that patients with contraindications to conventional allogeneic transplant experienced a high rate of transplant-related mortality after nonmyeloablative transplant.

Multiple myeloma, chronic lymphocytic leukemia; myelodysplastic syndrome

- The same limitations as the above indications were noted.

Patients with renal cancer or other tumors of solid organs

- Only 1 study of patients with renal cell carcinoma met the study selection criteria. However, the study size was small (n = 13) and the follow-up was short (median = 13 months). No data were reported by studies that met selection criteria on outcomes of nonmyeloablative transplant for other tumors of solid organs.

Annual updated literature searches through September 2003 have revealed additional phase I and II clinical trials, most of which have relatively few numbers of patients and short-terms outcomes. The largest study includes eighty-nine patients with hematologic malignancies considered to be at high risk for standard high-dose chemotherapy with allogeneic stem cell support. In this study, Maris and colleagues treated at-risk patients due to advanced age and/or comorbid conditions with nonmyeloablative allogeneic stem cell transplantation. Patients received stem cells from unrelated matched (n = 69) or mismatched (n = 16) donors. Recovery of neutrophil counts to acceptable levels was observed in 83 patients at a median time of 15 days post-transplant; 24 patients did not develop neutropenia from the nonmyeloablative chemotherapy. Platelet recovery occurred within 4 days; 49 patients did not develop thrombocytopenia from the nonmyeloablative regimen. Donor engraftment at day 28 was observed in 77 patients. The sustained engraftment rate was higher in patients receiving donor peripheral stem cells (85%) than those who received donor bone marrow derived stem cells (55%). New onset of alopecia, mucositis, or veno-occlusive disease was not seen in any patient. The median hospital stay was 8.5 days, with eight patients staying in overnight only for unrelated donor stem cell infusions. The accumulative incidence of grade III and grade IV GVHD was 11% (9% grade III, 2% grade IV). Chronic GVHD requiring therapy occurred in 40 patients. The cumulative probability of chronic extensive GVHD at one year for all 89 patients was 37%. Four patients without relapse died from complications arising from either acute or chronic GVHD. Median one-year survival was 52%. Progression-free survival at 1 year was 38%. The recipients of peripherally derived donor stem cell had a better overall survival and progression-free survival than patients who received bone marrow derived donor stem cells: 57% vs. 33%, (p = 0.13) and 44% vs. 17% (p = 0.02) respectively.

Studies in patients with solid tumors have also been published with promising, albeit preliminary results. For example, Bregni and colleagues treated 6 patients with advanced breast cancer and 7 patients with advanced renal cell carcinoma with nonmyeloablative chemotherapy followed by allogeneic stem cell transplant. In this small series of patients with late stage disease, there were no complete responders and six partial responders. All patients achieved complete neutrophil and platelet engraftment, and on day 60, bone marrow chimerism was more than or equal to 80% in 12 patients. Rini et al. treated 15 patients with metastatic renal cell carcinoma with nonmyeloablative chemotherapy, followed by allogeneic stem cell transplantation. Six-month outcomes were reported for twelve patients. All patients achieved sustained

Non-Myeloablative Human Stem Cell Transplants (BMT or HSCT) or "Mini-Transplants, continued

donor engraftment, 4 achieved a partial response, 2 patients developed acute graft versus host disease (GVHD), 6 developed chronic GVHD, and 4 died of transplant-related complications. These studies address the feasibility of a nonmyeloablative regimen, and that donor engraftment can be achieved with adequate immunosuppression. However, results do not include complete response rates or survival data, which are the outcomes of interest.

Tandem Transplant

A Medline search of the literature through September 2003 returned 1 study addressing tandem transplants using high-dose chemotherapy with autologous stem cell transplant (HDC/AuSCS), followed by nonmyeloablative allogeneic stem cell transplant. Carella et al. treated 15 patients with Hodgkin's disease or non-Hodgkin's lymphoma with primary refractory disease or relapsed disease. There was a median of 61 days between therapies. Following HDC/AuSCS there were 3 complete responders and 12 partial responders. Following nonmyeloablative allogeneic stem cell transplant ,9 partial responders became complete responders, 2 developed progressive disease, 2 of the initial complete responders continued to have a complete response and 1 complete responder became a partial responder. Seven of the patients required additional donor leukocyte infusions for complete chimerism. At a median 12 months of follow-up, 7 patients were alive in complete response, 2 were alive but in relapse, 2 died of progressive disease, and 2 died with extensive GVHD. Four of the 7 complete responders were experiencing acute GVHD. This study addresses the feasibility of a tandem regimen; however, follow-up is too short to determine the outcomes of the graft-versus-tumor effect that is proposed to improve chances of survival in refractory and relapsed patients with Hodgkin's disease and non-Hodgkin's lymphoma. There are no published studies comparing HDC/AuSCS alone to tandem HDC/AuSCS followed by nonmyeloablative allogeneic stem cell transplant or to other conventional therapies. Therefore, firm conclusions concerning improved survival, including morbidity and mortality associated with the nonmyeloablative allogeneic stem cell therapy, cannot be made.

Billing/Coding Information

CPT Codes

Not covered: Investigational/Experimental/Unproven for this indication

38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38241	Bone marrow or blood derived peripheral stem cell transplantation, autologous

Covered: For the conditions outlined above

38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition.
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	; thawing of previously frozen harvest, without washing
38209	; thawing of previously frozen harvest, with washing
38210	; specific cell depletion within harvest, T-cell depletion
38211	; tumor cell depletion
38212	; red blood cell removal
38213	; platelet depletion
38214	; plasma (volume) depletion
38215	; cell concentration in plasma, mononuclear, or buffy coat layer
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38242	Allogeneic lymphocyte infusions

Non-Myeloablative Human Stem Cell Transplants (BMT or HSCT) or "Mini-Transplants, continued

HCPCS CODES

S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition
Q0083	Chemotherapy administration by other than infusion technique only (e.g. subcutaneous, intramuscular, push), per visit
Q0084	Chemotherapy administration by infusion technique only (e.g. subcutaneous, intramuscular, push), per visit
Q0085	Chemotherapy administration by both infusion technique and other technique(s) (e.g. subcutaneous, intramuscular, push), per visit

Key References

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MEDICAL POLICY

PROTON BEAM THERAPY

Policy # 456
Implementation Date: 8/16/10
Review Dates: 8/15/13, 6/11/15, 6/16/16, 6/15/17, 7/20/18, 6/18/19, 6/14/20, 5/25/23, 12/5/24
Revision Dates: 5/12/14, 7/1/23

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Proton beam therapy (PBT) is a type of radiation therapy that utilizes protons to deliver ionizing damage to a target. In conventional radiation, the greatest energy release is at the surface of the tissue and decreases exponentially the farther it travels. In contrast, the energy of a proton beam is released at the end of its path, a region called the Bragg peak. Since the energy release of the proton beam is confined to the narrow Bragg peak, collateral damage to the surrounding tissues should be reduced, while an increased dose of radiation can be delivered to the tumor.

These physical properties of PBT make it especially useful for cancers located in areas of the body that are highly sensitive to radiation and/or where damage to healthy tissue would be an unacceptable risk to the patient. In addition, PBT may also benefit patients with tumors that are not amenable to surgery. Therefore, PBT, either alone or in combination with conventional photon radiation, has been suggested for the treatment of malignancies such as intracranial arteriovenous malformations (AVMs), intracranial cavernous malformations, intracranial tumors, esophageal cancer, lung cancer, vestibular schwannomas and acoustic neuromas, and cervical cancer. The use of protons as a form of SRS is in limited use in the United States, as there are a limited number of institutions in the U.S. with proton accelerators and stereotactic targeting equipment.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers Proton Beam Therapy for the following conditions:

1. Chordomas and chondrosarcomas of the base of the skull, localized and in the postoperative setting
2. Uveal melanoma, when proton beam therapy is considered preferential, compared to brachytherapy
3. Select cases of localized unresectable hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma
4. Stage IIA seminoma
5. Malignancies requiring craniospinal irradiation (CSI)
6. Proton beam therapy is considered medically necessary for the treatment

Select Health

Proton Beam Therapy, continued

of pediatric malignancies

7. Proton beam therapy for the curative treatment of the following cancers is considered not medically necessary:
   a) Locally advanced breast cancer when treating the internal mammary nodes
   b) Primary central nervous system (CNS) cancer
   c) Esophageal cancer
   d) Head and neck cancer (excluding T1-T2N0M0 laryngeal cancer)
   e) Remaining cases of unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma
   f) Hodgkin's lymphoma
   g) Non-Hodgkin's lymphoma
   h) Stage III non-small cell lung cancer
   i) Pancreatic cancer
   j) Prostate cancer (unoperated)
   k) Retroperitoneal sarcoma
   l) Thymomas and thymic carcinoma

Select Health considers Proton Beam Therapy to be experimental/investigational due to a lack of evidence, for all other tumors, including the adjuvant or salvage treatment of prostate cancer (i.e., after prostatectomy).

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

Proton beam therapy (PBT) is a type of radiation therapy that utilizes protons to deliver ionizing damage to a target. In conventional radiation, the greatest energy release is at the surface of the tissue and decreases exponentially the farther it travels. In contrast, the energy of a proton beam is released at the end of its path, a region called the Bragg peak. Since the energy release of the proton beam is confined to the narrow Bragg peak, collateral damage to the surrounding tissues should be reduced, while an increased dose of radiation can be delivered to the tumor.

These physical properties of PBT make it especially useful for cancers located in areas of the body that are highly sensitive to radiation and/or where damage to healthy tissue would be an unacceptable risk to the patient. In addition, PBT may also benefit patients with tumors that are not amenable to surgery.

Select Health

Proton Beam Therapy, continued

Therefore, PBT, either alone or in combination with conventional photon radiation, has been suggested for the treatment of malignancies such as intracranial arteriovenous malformations (AVMs), intracranial cavernous malformations, intracranial tumors, esophageal cancer, lung cancer, vestibular schwannomas and acoustic neuromas, and cervical cancer.

The issues related to coverage of proton beam therapy as a treatment of various medical conditions is not isolated to the safety and efficacy of the therapy. Given the greatly increased costs of this therapy compared to standard electron beam therapy, it is equally important to assess the cost-effectiveness of proton beam therapy compared to other therapies used to treat similar conditions.

In 2004, Hayes, Inc. published 3 systematic reviews on proton beam therapy. The following conclusions were offered:

- Proton Beam Therapy (May 2004) -- Available scientific evidence indicates that proton beam therapy has clinical utility in the treatment of intracranial AVMs. Questions remain with respect to definitive patient selection criteria, comparative efficacy relative to other forms of treatment, and optimal treatment protocols.
- Prostate Cancer (May 2004) -- Although a number of patients with prostate cancer have been successfully treated with proton beam therapy, significant questions remain. The lack of randomized controlled trials and the small number of trials directly comparing outcome of patients treated with proton beam therapy with those treated by conventional methods, such as radical prostatectomy and conformational three-dimensional photon therapy, should be addressed. In addition, relevant patient selection criteria for proton beam therapy for prostate cancer have not been established. In light of the high start-up costs of a medical synchrotron and proton beam therapy facility, a need exists for formal cost-benefit analysis.
- Ocular Tumors, Hemangiomas, and Macular Degeneration (July 2004) -- There is moderate evidence obtained from large-scale, uncontrolled studies indicating that PBT has clinical utility in the treatment of melanomas of the uveal tract. Although lack of control or comparative treatment groups limit the quality of most studies, it has to be taken into consideration that most of these patients have few other treatment options, and if left untreated, these conditions would result in complete loss of vision or require enucleation, or the patients could die secondary to distant metastasis. Therefore, the increase in patient survival, tumor control, and eye-retention observed in these studies can be attributed to the treatment. However, questions remain regarding patient selection criteria, efficacy compared with standard radiation therapy, and cost-effectiveness. There is a paucity of evidence regarding PBT for AMD or choroidal hemangioma, and no conclusions can be drawn regarding the safety, efficacy, or appropriate clinical role of PBT for these conditions.

The literature, however, fails to demonstrate comparable efficacy or safety to standard therapy in most instances. Given this lack of clinical trials, the use of expert opinion, though a lower level of evidence, seems reasonable to determine the appropriate use of the more expensive proton beam therapy. Input received from the Intermountain Oncology Clinical Program, particularly the radiation oncologists, suggests that except in rare circumstances such as chordomas, nonresectable salivary gland tumors, uveal melanomas, and some AVMs, this therapy has not demonstrated significant clinical advantages over currently available alternative therapies.

An updated technology assessment performed in May 2010 identified 18 peer reviewed papers and 4 systematic reviews since the last assessment. The peer reviewed papers cover a variety of tumors including lung, prostate, eye, ear, liver, bladder, esophageal and sinus; all with mixed reviews. In most of these studies it was concluded that proton beam therapy was efficacious and safe. None of these studies were comparative to alternative radiation therapy modalities and were essentially composed of case series or cohort studies. Three of the papers indicate improved results if the patients were female and had small tumors. As per the size of the tumors, it is indicated that improved health outcomes are noticed after the use of PBT if the radiotherapy is performed early. Some papers illustrated non-conventional techniques including hypo-fractioning the treatments, which has been demonstrated to be unnecessary.

In contrast to these studies, a systematic review completed by AHRQ in 2009 and Hayes, reports on several conditions including prostate cancer and concluded the evidence was insufficient to determine any advantage of this therapy compared to standard techniques and long-term outcomes data was lacking. It was also felt that the various authors' conclusions may reflect author bias due to their personal

Proton Beam Therapy, continued

investment in this modality of treatment. The AHRQ review concluded: "… no study found that charged particle radiotherapy is significantly better than alternative treatments with respect to patient-relevant clinical outcomes."

With regards to the use of PBT in prostate cancer, the evidence remains equally inadequate. No study to date has demonstrated superior long-term outcomes related to PBT compared to alternative therapies to treat localized disease. The Hayes directory report from 2006 specifically concluded: "While there is some evidence that PBT is safe and can provide effective tumor control in patients with prostate cancer, much of this evidence has been derived from retrospective analyses conducted at a limited number of research facilities or from studies with other methodological limitations. The lack of randomized controlled trials and the small number of trials directly comparing outcomes of patients treated with PBT with those treated by conventional methods, such as radical prostatectomy and conformational three-dimensional photon therapy, should be addressed. In addition, although most studies involved patients with early-stage disease, definitive patient selection criteria for PBT for prostate cancer have not been established. Finally, considering the high start-up costs of a clinical proton beam treatment facility, a need exists for formal cost-benefit analysis." No subsequent studies have refuted these conclusions.

Though proponents of photon beam therapy point to the unique characteristics of this modality's ability to deliver energy to the target area more precisely, this claim remains theoretical as there are no randomized comparison studies of proton beam and photon beam in the treatment of prostate cancer or other cancers/indications from which reasonable conclusions can be drawn related to efficacy and safety. No inference about the efficacy of proton therapy vis-à-vis photon therapy can be made given the current body of literature.

Billing/Coding Information

CPT CODES

77520 Proton treatment delivery; simple, without compensation

77522 Proton treatment delivery; simple, with compensation

77523 Proton treatment delivery; intermediate

77525 Proton treatment delivery, complex

77301 Intensity modulated radiation therapy plan, including dose volume histogram for target and critical structure partial tolerance specifications (IMRT treatment plan)

77295 3-dimensional radiotherapy plan, including dose-volume histograms (3D conformal treatment plan)

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Proton Beam Therapy, continued

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Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated coverage criteria to align with current clinical standards.

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MEDICAL POLICY

SELECTIVE INTERNAL RADIATION THERAPY (SIRT, RADIOEMBOLIZATION)

Policy # 308

Implementation Date: 6/6/06
Review Dates: 10/18/07, 12/18/08, 12/19/09, 12/16/10, 8/16/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 7/20/18, 6/18/19, 6/14/20, 8/19/21, 7/26/22, 8/16/23, 8/12/24
Revision Dates: 9/30/06, 7/11/11, 12/7/15, 9/18/19, 8/23/24

Description

Hepatic tumors can arise either as primary liver cancer or by metastasis to the liver from other tissues or organs. Unfortunately, most hepatic tumors are unresectable at diagnosis, due either to their anatomic location, size, number of lesions, concurrent nonmalignant liver disease, or insufficient hepatic reserve. Palliative treatment with combined systemic and hepatic artery infusion (HAI) may increase disease-free intervals for patients with unresectable hepatic metastases from CRC. However, durable responses to chemotherapy are less likely for patients with unresectable primary hepatocellular cancer (HCC).

Adenoid cystic carcinoma (AdCC) is a rare cancer, typically originating in the head and neck region that can metastasize to the liver. This malignancy has a slow and sometimes relentless progression, with a tendency to grow along nerves. High rates of local recurrence and a predilection to metastasize to the lungs and liver lead to a poor prognosis beyond 10 years. Metastasis can occur even a decade or more after initial treatment of the primary. AdCC is most often diagnosed in people in their 40s to 60s. Due to its slow growth, AdCC has a relatively indolent but relentless course. Unlike most carcinomas, many with AdCC survive for 5 years, only to have tumors recur and progress.

Selective internal radiation therapy (SIRT) irradiates malignant liver lesions using microscopic beads. This unique, targeted therapy spares healthy tissue while delivering up to 40 times more radiation to the liver tumors than would be possible using conventional radiotherapy. Conventional radiotherapy can only be applied to limited areas of the body, and it adversely affects nearby tissues. SIRT, on the other hand, involves the delivery of millions of microscopic radioactive spheres directly to the site of the liver tumors, where they selectively irradiate the tumors.

The spheres are delivered through a catheter placed in the femoral artery of the upper thigh and threaded through the hepatic artery to the site of the tumor. The microscopic spheres, each approximately 35 microns (one-third the diameter of a strand of hair), are bonded to yttrium-90 (^{90}Y). The amount of ^{90}Y decreases by 50% every 2.5 days within the patient. The microspheres are trapped in the tumor's vascular bed, where they destroy the tumor by reducing its blood supply (embolic effect) and through local radiotherapy damage to the cancer cells' DNA. The radiation is wholly contained within the patient's body and is continually delivered over approximately 2 weeks, at which point the microspheres are no longer radioactive.

Unlike chemotherapy, which is administered in regular repetitive cycles, SIRT may be administered to the patient in a single up to several treatments, separated by an unspecified period, and to varying volumes of liver. SIRT may treat a lobe, segment, or subsegmental area of the liver as dictated by the disease volume and its blood supply. Treatment is considered outpatient and normally patients go home within 24 hours.

Select Health

Selective Internal Radiation Therapy (SIRT, Radioembolization), continued

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers selective internal radiation therapy (SIRT) using intra-arterial injection of radiolabeled microspheres *only* for the following conditions:

1. Unresectable primary hepatocellular carcinoma
2. Unresectable metastatic liver tumors from primary colorectal cancer
3. Hepatic metastases from neuroendocrine tumors with diffuse and symptomatic disease when systemic therapy has failed to control symptoms
4. Hepatic metastases from uveal melanoma

Select Health does NOT cover selective internal radiation therapy (SIRT) using intra-arterial injection of radiolabeled microspheres in the treatment of any other indications, including adenoid cystic carcinoma (AdCC). There is a lack of literature to demonstrate the efficacy and safety of selective internal radiation therapy for other indications; this meets the plan's definition of experimental/investigational.

SELECT HEALTH ADVANTAGE (MEDICARE/CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The literature related to SIRT is greatly limited, in part, by the relatively few clinical opportunities where it is appropriate to apply this technology. Nonetheless, of the 30 studies identified for this review, only 3 were randomized trials comparing SIRT with other therapeutic options, 3 of which involved SIR-Spheres in patients with hepatic metastases from colorectal cancer. The remainders were primarily small, uncontrolled prospective and retrospective reports in which there was substantial variability in patient populations and treatment protocols.

Metastatic liver tumors of colorectal cancer: Gray et al. randomly assigned 70 patients with non-resectable liver metastases from primary adenocarcinoma of the large bowel to 1 of 2 treatment options: 1) hepatic artery chemotherapy (HAC) with floxundine, or 2) the same chemotherapy plus a single injection of SIR-Spheres. Only patients with non-resectable metastases limited to the liver and lymph nodes in the porta hepatis were included. Patients in whom the liver metastases could be treated by any form of local ablation such as surgical resection or cryotherapy were excluded.

Relative to the control group, SIR-Spheres patients experienced higher rates of partial and complete response as measured by tumor area, tumor volume, and serum carcino-embryonic antigen (CEA). Specifically, more than twice as many patients receiving SIRT (44% vs. 17.6%) achieved either a complete (disappearance of all tumor on two successive CAT scans at least 3 months apart OR decrease in serum CEA into the normal range) or partial response (50% decrease in tumor size on 2 successive

Select Health

Selective Internal Radiation Therapy (SIRT, Radioembolization), continued

CAT scans at least 3 months apart OR decrease in serum CEA by ≥ 50%, but not into the normal range). Regardless of the measure used to indicate disease progression, SIR-Spheres patients experienced a longer median time to disease progression in the liver compared to chemotherapy controls (tumor area [15.9 vs. 9.7 months], tumor volume [12.0 vs. 7.6 months], or CEA [6.7 vs. 5.7 months]). The study was underpowered to show significant improvement in survival, but the Kaplan-Meier curve showed a trend towards increased survival for patients treated with SIRT, compared with those receiving HAC alone. The hazard ratios suggested that patients receiving chemotherapy alone have approximately a 40% higher death rate than for patients receiving SIRT plus chemotherapy. A larger trial is needed to demonstrate statistical significance of this survival benefit.

A study by Moroz et al. involved a similar design. Thirty-seven patients were randomized to undergo a similar chemotherapy regimen or to chemotherapy plus SIRT. After 12 months, hepatic volume decreased by 17% in SIRT patients but remained unchanged in controls. Both groups experienced a similar decrease in portal vein diameter (9%) and significant increases in spleen volume (48% and 26%). Van Hazel's randomized study involved 21 patients with previously untreated colorectal cancer metastases to the liver. The patients were randomized to the same chemotherapy regimen described above or to chemotherapy and SIR-Spheres. Compared to controls, the response rate for SIRT patients was higher as was the median survival (29.4 vs.12.8 months).

Stubbs et al. estimated survival for these patients in two prospective studies. The first, followed 38 patients with hepatic metastases who were treated with SIR-Spheres and reported survival at 6, 12, and 18 months was 70%, 46%, and 46%, respectively. The second study involved a larger group of metastatic patients that included the same 38 patients described above. In patients with extrahepatic disease within 6 months of SIRT, median survival was 6.9 months (1.3−18.8 months) and estimated survival at 6, 12, and 18 months was 57.7 ± 3.8%, 23.1 ± 4.8%, and 0%, respectively. In patients without extrahepatic disease, median survival was 17.5 months (1.0−30.3 months) with estimated survival at 6, 12, 18, 24, and 30 months of 79.2 ± 2.9%, 66.7 ± 3.6%, 55.9 ± 3.3%, 25.2 ± 4.4%, and 16.8 ± 5.0%, respectively.

Hepatocellular carcinoma: The only FDA approved microspheres for primary hepatocellular carcinoma are Theraspheres. However, approval under a Humanitarian Device Exemption released investigators from the requirement to demonstrate effectiveness. Such exemptions are granted to treatments intended for conditions that affect fewer than 4,000 individuals in the U.S. Consequently, there are no published randomized controlled trials involving Theraspheres. Several prospective studies have been published, the largest being a report by Salem et al., who described the treatment experience of approximately 300 patients with HCC at 8 U.S. medical institutions. This retrospective report did not offer additional details on patient characteristics or inclusion or exclusion criteria for treatment. Investigators described several minor GI side effects and indicated that more serious events had occurred, though details and specific numbers were not provided. Reported median survival of 54 patients with Okuda stage I or II HCC was 23 months (95% CI = 14, 44) and 11 months (95% CI = 6, 26), respectively. Overall survival at 1-year was 68% and 37%, respectively.

Carr et al. followed 65 patients who underwent SIRT and found that 65% experienced a significant decrease in tumor vascularity within 4 months of treatment. Median survival was 649 days (range 360−1012 days) in Okuda stage I patients and 302 days in Okuda stage II patients. In Geschwind et al., 80 patients with non-resectable HCC underwent SIRT. Of these, 23 (29%) had 2 SIRT treatments, 4 (5%) had 3 treatments, and 1 patient had 4 treatments. Median survival and the 1-year survival rates were 628 days and 63% for Okuda stage I patients and 384 days, and 51% for Okuda stage II patients. Nine patients experienced life-threatening or fatal events judged as possibly related to SIRT. These adverse events included increased prothrombin time, elevated serum bilirubin, hepatic encephalopathy, liver failure, cholecystitis, edema, and aspiration pneumonia.

The lack of randomized controlled trials, particularly those comparing SIRT with other treatment options, limits conclusions about whether SIRT is any more effective than other treatment modalities for HCC or hepatic metastases. A lack of long-term follow-up data further limits comparability of survival associated with SIRT to other non-surgical forms of therapy. The 1 SIRT study with long-term survival estimates was underpowered to detect a survival benefit. The longest follow-up period located in this review was 30 months, while 5-year survival data are available for other non-surgical therapies. The available survival data suggest that SIRT does improve short-term survival over chemotherapy alone, but these estimates appear to be markedly lower than survival with other treatments. However, survival varies with the progression of the cancer and patients with less advanced cancer faring better than those with more

Select Health

Selective Internal Radiation Therapy (SIRT, Radioembolization), continued

advanced tumors. Comparing survival estimates across studies is problematic, however, there is substantial heterogeneity in how study populations are defined and treated, and in how therapies are applied. Again, comparative trials are necessary to truly evaluate the effect of SIRT relative to other therapeutic options.

Metastatic Neuroendocrine tumors: Paprottka et al. studied 42 patients with treatment refractory NETLM. Imaging follow-up using RECIST at 3-month follow-up demonstrated partial response, stable disease, and progressive disease in 22.5, 75.0, and 2.5% of patients, respectively. In 97.5% of patients, the liver lesions appeared hypovascular or partially necrotic. The mean follow-up was 16.2 months with 40 patients (95.2%) remaining alive. The median decrease in tumor-marker levels at 3 months was 54.8% (chromogranin A) and 37.3% (serotonin), respectively. There were no acute or delayed toxicities greater than grade 2. Improvement of clinical symptoms 3 months after treatment, was observed in 36 of 38 symptomatic patients.

Peger et al. studied 30 patients with unresectable NETLM. The mean follow-up was 23.0+/-19.4 months and the median overall survival was 39 months (95% CI, 12.6−65.4 months), with one- and two-year survival rates of 71% and 45%, respectively. Imaging follow-up using RECIST at three-month intervals demonstrated partial response in 43%, complete remission in 3%, stable disease in 37%, and progressive disease in 17% of patients. Extent of tumor involvement was found to have a statistically significant influence on overall survival (P = 0.03). The existence of extrahepatic disease at the time of radioembolization, radiographic response, age, and primary neuroendocrine tumor site were not significant prognostic factors.

Adenoid cystic carcinoma (AdCC): No systematic reviews or primary studies concerning SIRT as a treatment for adenoid cystic carcinoma were identified in the published peer-reviewed literature. What reviews and peer-reviewed literature do exist only speak of SIRTs use in general metastatic disease to the liver, typically, colorectal metastases.

In addition to the lack of published literature related to the effectiveness and safety of SIRT on metastatic adenoid cystic carcinoma, Laramore et al. noted: “Adenoid cystic carcinomas most often respond slowly to radiotherapy, and one would not expect much tumor shrinkage before the surgery.” This suggests use of SIRT even in investigational settings may have a low probability of a successful outcome.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
77778	Interstitial radiation source application; complex
79445	Radiopharmaceutical therapy, by intra-articular administration

HCPCS CODES

C2616	Brachytherapy source, yttrium-90, per source
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres

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Selective Internal Radiation Therapy (SIRT, Radioembolization), continued

Revision History

Revision Date	Summary of Changes
8/23/24	For Commercial Plan Policy, specified adenoid cystic carcinoma (AdCC) is considered as an exclusion for this treatment.

Select Health

MEDICAL POLICY

STEREOTACTIC RADIATION THERAPY

Policy # 336

Implementation Date:1/21/06

Review Dates: 5/17/07, 4/24/08, 8/16/12, 8/15/13, 6/19/14, 6/11/15, 6/16/16, 6/15/17, 8/7/18, 10/14/19, 5/25/23, 12/5/24

Revision Dates: 8/1/07, 1/12/09, 2/18/10, 2/17/11, 7/11/11, 7/27/17, 5/2/19, 7/1/23, 11/11/24

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Stereotactic radiosurgery (SRS), also known as stereotactic radiation therapy (SRT) or stereotactic body radiotherapy (SBRT), targets a tumor from many different directions so the beams of radiation converge on the tumor. No actual incision is made in SRS/SRT/SBRT (hereafter known simply as SBRT). The goal of SBRT is to deliver enough radiation to destroy or stop the growth of a lesion without adversely affecting surrounding tissue. Normal tissues are protected both by selectively targeting only the abnormal lesion and by using cross-firing techniques to minimize the exposure of the adjacent anatomy. In that way, the correct amount of radiation needed to destroy tumor cells is delivered directly to the neoplasm, and the amount of exposure to the area surrounding the tumor is limited. With SBRT, high doses of radiation can be delivered with sub-millimeter accuracy. Although SBRT uses immobilization, with the assistance of removable masks and frames, and three-dimensional imaging with computer-aided planning, at a cellular level, the mechanism of action is the same as in all other forms of radiation treatment (i.e., distorting the DNA of the tumor cells and interfering with replication and cell growth.)

Radiosurgery has potential advantages over open surgery in that it is not invasive and can more easily address inaccessible or multiple lesions. In addition, the border zone between the lesion and normal tissue may receive a radiation dose sufficient to decrease the risk of local recurrence. The 2 major disadvantages of radiosurgery are that it generally is applicable only to lesions less than about 2.5−3.0 cm in diameter and that it results in slow tumor shrinkage over weeks or months rather than relieving mass effect immediately. The primary risk of radiosurgery is radiation necrosis, which may occur 6−24 months after treatment and is related to the dose delivered and the volume treated.

Fractionated or staged SRS is referred to as stereotactic radiotherapy (SRT). SRT is a process in which the total radiation dose that would be used with SRS is "hyperfractionated," or divided into several smaller doses, with each dose delivered on a separate day. SRT permits radiation to be delivered at an overall higher dose and over larger areas than is possible with SRS. Because the treatment is given over consecutive days in smaller daily doses, normal tissues are spared. Therefore, fractionated radiosurgery is frequently used for brain tumors near the optic chiasm (e.g., pituitary tumors) or for tumors that surround normal nerves (e.g., acoustic neuromas and meningiomas of the cavernous sinus or skull base). Stereotactic radiosurgery (SRT) is used to treat lesions on the brain, while stereotactic body radiotherapy (SBRT) is used to treat lesions in the body.

In many situations, SBRT are planned and supervised by a neurosurgeon and a radiation oncologist working together. This care may also be supervised only by a radiation oncologist. During the procedure, the patient's head is held perfectly still by a temporary frame surgically attached to the skull. Then, using a map based on images of the tumor and the brain obtained from computed tomography (CT) scans, magnetic resonance imaging (MRI), and/or arteriography, a computer guides a movable radiation therapy machine that delivers beams of radiation to the brain tumor from many different angles. This is usually performed on an outpatient basis but may require admission to an observation setting.

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Stereotactic Radiation Therapy, continued

There are 2 basic forms of SRS: linear-accelerator (LINAC) based, and Cobalt 60-based (i.e., gamma ray photons). The use of protons as a form of SRS is in limited use in the United States, as there are only a limited number of institutions in the U.S. with proton accelerators and stereotactic targeting equipment.

LINAC-based systems use x-ray beams generated from a linear accelerator. As a result, these devices do not require or generate any radioactive material. They deliver high-energy x-ray photons or electrons in curving paths around the patient's head. LINAC is more widely available and can be used to deliver fractionated treatment and is able to use a larger x-ray beam, which enables it to treat larger tumors more uniformly and with less repositioning. Intensity modulated radiation therapy (IMRT) is a LINAC-based technology using computer-controlled "beam-shaping."

The CyberKnife System is a LINAC SRS system using a miniature linear accelerator mounted on a flexible robotic arm and several x-ray cameras that are combined with software to track patient position. The cameras obtain frequent pictures of the patient during treatment and use this information to target the radiation beam emitted by the linear accelerator. No immobilization device is required. However, there is need for placement of very small markers via a needle for the treatment of targets outside of the head.

The CyberKnife System for stereotactic radiosurgery/radiotherapy was approved by the FDA in 1999 for use in the head and neck above the cervicothoracic junction. In 2001, CyberKnife with Dynamic Tracking Software (DTS) was approved to provide radiosurgery for lesions, tumors, and conditions anywhere in the body when radiation treatment is indicated.

Cobalt 60-based (photon) systems (e.g., the Gamma Knife) are a stereotactic radiosurgery treatment that uses gamma rays from radioactive cobalt-60 sources focused on the tumor using 201 multiple small beams. Because of its high accuracy, it is usually used on small- to medium-sized lesions, whereas LINAC is usually used for larger lesions. Multiple targets in the brain can be treated during a single treatment session. It cannot be used for fractionated radiosurgery (FRS). It is designed to treat intracranial targets only. These machines are ideal for smaller tumors and lesions and for functional disorders of the brain. The Gamma Knife loses its ability to spare surrounding normal tissues as the number of targets increases. It is not suitable for targets larger than 3−4 cm in size. It is not used for targets outside of the head.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers stereotactic radiation therapy, including stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), for the following indications:

1. Acoustic neuroma (vestibular schwannoma);
2. Brain metastasis, when one of the following criteria are met:
   a) Newly diagnosed brain metastasis, and all the following criteria are met:
      i. Individual has a good performance status (Karnofsky Performance Status [KPS] score ≥ 70% or Eastern Cooperative Oncology Group [ECOG] performance status of 0-2); and
      ii. Absence of leptomeningeal metastases; and
      iii. Individual does not have a diagnosis of lymphoma, germ cell tumor, or small cell carcinoma.
      iv. Has up to 10 lesions or cumulative tumor volume of < 15cc
   b) Individual is undergoing repeat stereotactic radiation therapy, when all the following criteria are met:
      i. Individual has a good performance status (KPS score ≥ 70% or ECOG

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Stereotactic Radiation Therapy, continued

performance status of 0-2); and

ii. Absence of leptomeningeal metastases; and

iii. Stable extra-cranial disease as documented on restaging studies dated within the past two months; and

iv. Total number of brain metastases treated in the past 12 months is ≤ 13.

c) Retreatment after previous whole brain radiation therapy

3. Chordoma and chondrosarcoma
4. Craniopharyngioma
5. Definitive treatment of the following:
   a) Hepatocellular carcinoma without evidence of regional or distant metastasis
   b) Non-small cell lung cancer, when all the following criteria are met:
      i. Stage I or stage IIA with negative mediastinal lymph nodes; and
      ii. Tumor size ≤ 5cm; and
      iii. Individual is medically inoperable or refuses to have surgery after thoracic surgery evaluation.
   c) Pancreatic adenocarcinoma without evidence of distant metastasis
   d) Prostate cancer without evidence of distant metastases
6. Extracranial oligometastatic disease, when all the following criteria are met:
   a) Primary tumor type is any of the following:
      i. Colorectal cancer
      ii. Melanoma
      iii. Non-small cell lung cancer
      iv. Prostate cancer
      v. Renal cancer
      vi. Sarcoma; and
   b) Controlled primary tumor defined as at least 3 months since original tumor was treated definitively, with no progression at primary site; and
   c) Performance status KPS score ≥ 70% or ECOG performance status of 0 – 2; and
   d) Has up to 5 metastatic lesions, and if the individual has previously received local therapy (e.g., SBRT, surgery, or radiofrequency ablation) for metastatic disease, the treated lesion(s) from that therapy are included in the total count of 5 lesions; and
   e) Each lesion is ≤ 5 cm in size; and
   f) No evidence of malignant pleural effusion, leptomeningeal or peritoneal carcinomatosis.
7. Glomus jugulare tumors
8. Hemangiomas of the brain
9. Intracranial arteriovenous malformations (AVMs)

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10. Meningioma
11. Pineal gland tumors
12. Pituitary adenoma
13. Recurrent gliomas
14. To treat a previously irradiated field
15. Trigeminal neuralgia refractory to medical therapy
16. Uveal melanoma

Repeat SRS/SBRT will be considered not medically necessary within 3 months of the first course of therapy.

Select Health considers stereotactic radiation therapy, including stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) to be experimental/investigational for all other indications.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For this policy, specifically, there are no CMS criteria available; therefore, the Select Health Commercial policy or InterQual criteria apply. Select Health applies these requirements after careful review of the evidence that supports the clinical benefits outweigh the clinical risks. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

SRS is primarily performed on the head and neck, as these areas can be immobilized with skeletal fixation devices that completely restrict the head's movement, permitting the most precise and accurate treatment. SRS is a therapeutic option for many types of brain conditions, especially for tumors and blood vessel abnormalities located deep within or close to vital areas of the brain. Some examples of established SRS use include metastatic tumors, malignant gliomas, benign brain tumors, AVMs, and trigeminal neuralgia. More than 90% of metastatic tumors are initially controlled with SRS, and 80% are controlled long-term. SRS has the greatest impact on survival in patients with single brain metastases, but it is also suitable for patients with multiple lesions and controlled primary disease, as well as for patients with recurrence in the brain at distant sites. Patients with trigeminal neuralgia are frequently elderly and are often not fit for conventional surgery. Eighty percent to 85% of patients have significant improvement in their pain following SRS, but as many as 40% recur within 5 years. SRS has been used both as an alternative to, and in combination with, conventional radiation and/or surgery.

One research focus has been on the treatment of acoustic neuromas, the most significant side effect of greatest concern in this population is functional preservation of the facial and auditory nerve. For example, in a single institution study, Meijer and colleagues reported on the outcomes of single fraction vs. fractionated LINAC-based stereotactic radiosurgery in 129 patients with acoustic neuromas. Among these patients, 49 were edentate and thus could not be fitted with a relocatable head frame that relies on dental impressions. This group was treated with a single fraction, while the remaining 80 patients were

Stereotactic Radiation Therapy, continued

treated with a fractionated schedule. With an average follow-up of 33 months, there was no difference in outcome in terms of local tumor control, facial nerve preservation, and hearing preservation. Chung et al. reported on the results of a single institution case series of 72 patients with acoustic neuromas, 45 who received single fraction therapy and 27 who received fractionated therapy. Fourteen patients receiving single fraction treatment were functionally deaf, while those receiving fractionated therapy had useful hearing in the affected ear. After a median follow-up of 26 months, there was no tumor recurrence in either group. Three separate single-institution case series reported on 87 patients with metastatic disease, 143 patients with astrocytomas, and 36 patients with cerebral AVMs who were treated with fractionated stereotactic radiosurgery. While all reported promising outcomes, the lack of a control group receiving stereotactic radiosurgery in a single session limits interpretation.

Aoyama et al., in 2006, reported on a randomized trial of SRS plus whole brain radiation therapy (WBRT), versus SRS alone for treatment of patients with 1−4 brain metastases. They found a 12-month intracranial tumor recurrence rate of 46.8% in the SRS+WBRT group compared to 76.4% in the group that received only SRS. However, median survival times were not different at 7.5 and 8.0 months, respectively. They also found no difference in neurological functional preservation. In an accompanying editorial, Raizer comments that either treatment approach is a reasonable first step recognizing that those who select SRS alone are more likely to need subsequent salvage radiation treatments. Raizer adds the additional comment that those who have a single brain metastasis from non-small cell lung cancer or RPA (recursive partitioning analysis) class I patients should initially receive SRS and WBRT.

With regards to more controversial uses of STS, a prospective, Phase III multi-center study evaluated the efficacy and safety of Gamma Knife surgery in the treatment of drug-resistant epilepsy of mesial temporal lobe origin. A total of 21 patients from three centers underwent SRS. The authors reported the frequency of seizures was significantly smaller than that at the previous visit (reported at each 6-month follow-up evaluation). The median seizure frequency of 6.16 the month before treatment was reduced to 0.33 at 2 years following treatment. At 2 years, 65% of the patients (13 of 20) were seizure-free. Five patients had transient side-effects, including depression, headache, nausea, vomiting, and imbalance. There were no permanent neurological deficits reported, except 9 visual field deficits. No neuropsychological deterioration was observed 2 years after treatment. The authors reported that quality of life was significantly better than before surgery. The authors concluded that the safety and efficacy of radiosurgical treatment appears good in this group of patients over short-to-middle term timeframes. The authors stated that delay of the seizure cessation was the major disadvantage of Gamma Knife SRS. They noted a longer follow-up period is required for confirmation of these results. Both Barajas et al. and Selch et al. each reported on Gamma Knife surgery for hypothalamic hamartomas accompanied by medically-intractable epilepsy in three patients. Hypothalamic hamartoma is a nonneoplastic malformative mass of neurons and glia in the region of the hypothalamus. The authors both concluded that Gamma Knife SRS appears to be a good, safe, and effective option for the treatment of unresectable hypothalamic hamartomas. However, there is a lack of sufficient evidence in current peer-reviewed literature to support the use of SRS for patients with intractable seizures; a few, small, uncontrolled studies were identified. Large, controlled trials are needed to produce statistically significant data and radiosurgery treatment recommendations for patients with intractable seizures, including comparing the long-term safety and efficacy of SRS with other treatment options. No clinical trials were identified for the use of SRS in the treatment of obsessive-compulsive disorder. In 2004, Pallanti et al. reported that researchers had been studying neurosurgical approaches such as gamma knife capsulotomy to learn if these procedures are effective in treating treatment-resistant OCD. However, this same group noted more results are needed before the effectiveness of the nonpharmacological treatments for OCD can be determined.

With regards to use of SRS for cancers outside the CNS, Koong et al., in 2005, reported on a prospective Phase II clinical trial that evaluated the efficacy of conventional SRT followed by an SRS boost in 16 patients with locally advanced pancreatic cancer; two patients experienced Grade 3 toxicity. Fifteen of 16 patients were free from local progression until death; median overall survival was 33 weeks. The authors stated that concurrent IMRT and 5-FU followed by SRS in patients with locally advanced pancreatic cancer results in excellent local control but does not improve overall survival and is associated with more toxicity than SRS alone. As additional studies are lacking, large, controlled trials are needed to produce statistically significant data and radiosurgery treatment recommendations for patients with pancreatic cancer, including comparing the long-term safety and efficacy of SRS with other treatment options. King et al., in 2003, reported in a review of CyberKnife radiotherapy for localized prostate cancer that the

Stereotactic Radiation Therapy, continued

CyberKnife can produce superior dose volume histograms (DVHs) for sparing of rectum and bladder and excellent DVHs for target coverage compared with IMRT, and possesses dose heterogeneities to the same degree as IMRT plans. However, once again, large controlled trials are needed to produce statistically significant data and radiosurgery treatment recommendations for prostate cancer patients, including comparing the long-term safety and efficacy of SRS with other treatment options before a recommendation for use of this therapy for prostate cancer can be brought forward.

Le et al., in 2003, evaluated local tumor control in 45 patients with nasopharyngeal carcinoma who received SRS boost to the tumor site after external beam radiotherapy. Thirty-six received concurrent cisplatin-based chemotherapy. The 3-year local control rate was 100%; the freedom from distant metastasis rate was 69%; the progression-free survival rate was 71%; and the overall survival rate was 75%. The authors concluded that SRS boost after external beam radiotherapy provided excellent local control in nasopharyngeal carcinoma patients. In 2005, Iwai et al. reported on their study of 21 patients who had cavernous sinus metastases and invasion treated using Gamma Knife SRS and subsequent follow-up. Clinical symptoms were improved in 48% of the patients after treatment, and tumor growth control was obtained in 67% of the patients at their final follow-up. The actual 1- and 2-year tumor growth control rates were 68% and 43%, respectively. The mean survival time was 13 months. The authors stated that SRS is a very useful therapeutic option for the treatment of cavernous sinus metastases and invasion, either as initial treatment, or as an adjunct treatment for recurrences even in pre-irradiated patients. However, as only 2 other small case series studies could be identified and large, controlled trials are needed to produce statistically significant data and radiosurgery treatment recommendations for patients with nasopharyngeal cancer, including comparing the long-term safety and efficacy of SRS with other treatment options, it is felt there is a lack of sufficient evidence in current peer-reviewed literature to support the use of SRS for patients with nasopharyngeal cancer.

A December 2008 technology assessment found the only systematic review to have reviewed stereotactic radiosurgery (SRS) for treatment of lung tumors was a Hayes Directory from 2004. This report included NSCLC and lung metastases among the multiple indications for which robotic SRS could be utilized. The report gave a “D” rating for SRS for primary lung tumors or lung metastases in patients with advanced age, poor underlying lung function, or multiple co-morbidities. This rating reflects Hayes’ conclusion that the research regarding use of the SRS for this indication is so limited that an appraisal of safety and efficacy cannot be made.

Significant heterogeneity exists in the literature in terms of patient populations and treatment protocols. For example, total Gy administered ranged from 5 Gy to 6800 Gy based on stage, tumor size, and treatment response. Comparisons across trials are difficult as a result. Nevertheless, the literature suggests overall 1-year survival rates between 52%−100%; 2-year rates between 32%−91%; 3-year rates between 32%−72%; and 5-year rates between 17%−71%. Cancer specific survival rates also varied between 70%−96% at year 1; 49%−82% at year 2; and 49%−92%. Local control rates varied between 68%−100%. Several studies reported outcomes reported outcomes stratified by stage, tumor size, and tumor source (primary vs. metastatic), which generally suggest that outcomes are better for primary and smaller volume tumors, and early stage disease. The literature also suggests a dose response relationship between total Gy and tumor response.

None of these studies directly compared outcomes to those of other common therapies through a comparative trial, though most authors extrapolated from these data to conclude that the outcomes associated with this therapy are comparable. Indeed, these outcomes suggest that stereotactic radiosurgery does produce short-term outcomes similar to that observed with resection and external beam radiation. However, long-term data are lacking as outcomes are only reported out to five years in a few studies. Moreover, outcomes are highly dependent on total Gy, size of the tumor, and the stage of cancer, among other factors, suggesting that patient selection factors remain undefined for this therapy. Finally, though improved quality of life is ostensibly one motivation for offering this therapy, especially in patients with metastatic disease where improved survival is not anticipated, no studies directly assessed any quality of life outcome in any patient populations. Thus, use of this therapy as a substitute for standard therapies remains uncertain. For inoperable tumors, however, stereotactic radiosurgery may be a reasonable option.

SRS has also been proposed as a therapy for the treatment of Parkinson’s disease and other involuntary movement disorders. Ohye et al., in 2002, reported on 53 patients with Parkinson’s disease and other kinds of involuntary movement who underwent gamma thalamotomy. Eighty percent of the treated cases

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Stereotactic Radiation Therapy, continued

showed good results and no significant complications, with the tremor subsiding at one year. However, in this article the authors stated that gamma thalamotomy for functional disorders is still under development, but there are grounds for increasing optimism. In a smaller case series study of eight patients, Su et al. also reported on their results from a study performed in 2002 in which patients underwent stereotactic surgery on the subthalamic nucleus in patients with Parkinson's disease. The authors stated that subthalamotomy can ameliorate the cardinal symptoms of Parkinson's disease, reduce the dosage of levodopa, diminish complications of the drug therapy, and improve the quality of life. This somewhat contradicts the conclusions of Okun et al. They concluded: "… though many medical centers throughout the world offer radiosurgery for pallidotomy and thalamotomy as a safe and effective alternative to radiofrequency ablative surgery and deep-brain stimulation for Parkinson's disease, the reported incidence of significant complications varies considerably, and the long-term complication rate remains unknown." In essence, there is a lack of sufficient evidence in current peer-reviewed literature to support the use of SRS for patients with Parkinson's disease. Available evidence is limited to small case series; and large, controlled trials are needed to produce statistically significant data and radiosurgery treatment recommendations for Parkinson's disease patients, including comparing the long-term safety and efficacy of SRS with other treatment options.

Supporting the above conclusion, the American Association of Neurological Surgeons (AANS) lists use of SRS for patients with Parkinson's disease, epilepsy or some forms of psychoneurosis, such as obsessive-compulsive disorder as experimental. It noted several centers are undertaking trials to identify the utility of this therapy for these indications and may be treated on an experimental basis with SRS (AANS, 2000). This position is supported by the International RadioSurgery Association (IRSA) Stereotactic Radiosurgery Practice Guidelines. It specifically notes that for patients with intractable typical trigeminal neuralgia (TN), Gamma Knife SRS is effective and is a good treatment option for TN patients with co-morbidities, high-risk medical illness, or pain refractory to prior surgical procedures, because it is the least invasive procedure for TN. Gamma Knife surgery is usually the primary treatment for patients with co-morbidities and/or contraindications to other treatment options. Additionally, for patients with intracranial AVMs, it states that SRS is the treatment of choice for patients with unresectable AVMs. Because of the delayed obliteration rate of AVMs after radiosurgery, comprehensive long-term management and observational strategies are necessary. Results show a success rate of 50%−95% at the end of 3 years of observation after a single radiosurgery procedure. Finally, for patients with pituitary adenomas, it reports that fractionated radiation surgery has been used for the treatment of unresectable pituitary adenomas with tumor-control results, varying from 76%−97%. The guideline further states the major role of pituitary adenoma radiosurgery is as an adjuvant to surgical resection, although it has a primary role for selected cases at higher medical risk for general anesthesia, microsurgery, or cavernous sinus tumor involvement, as well as for patients who consciously choose not to undergo microsurgery.

The current peer-reviewed literature supports the use of stereotactic radiosurgery (SRS) for arteriovenous malformations not amenable to surgical resection, primary tumors of the brain, brain metastases, trigeminal neuralgia refractory to medical management, and inoperable spinal tumors with compression or intractable pain. There are U.S. Food and Drug Administration (FDA)-approved linear accelerator (LINAC)-based systems for extracranial use. Centers with CyberKnife and Trilogy technology are performing radiosurgery on extracranial tumors and lesions. Although promising, there are no large, controlled clinical trials clearly defining the long-term safety and efficacy of SRS in comparison to other radiotherapy treatments or other non-radiotherapy treatments for extracranial sites other than the spine (i.e., stereotactic body radiosurgery).

A literature review performed in February 2011 identified some data in support of SRS or SRT for limited liver metastases is also accumulating from multiple institutions, especially in the situation of colorectal cancer metastases, and breast cancer metastases, both of which have a relatively long natural history. A series from the University of Rochester of 174 metastatic liver lesions (various primary sites) showed infield local control rates of 76% and 57%, at 10 and 20 months, and overall median survival of 14.5 months with no grade 3 or higher toxicity. Investigators from Princess Margaret Hospital treated 68 patients with liver metastases who were not candidates for other therapy (most co10recta1 and breast) with SRT. They report a 1-year local control rate of 71% and median survival of 17.6 months. A prospective multi-institutional phase I/II study of 47 patients with 63 lesions yielded local control at 1 and 2 years of 95% and 92%, respectively, with only 3 lesions progressing at a median of 7.5 months. These authors concluded patients with 1−3 metastases were good candidates for this method of treatment. A pooled analysis of patients treated at Princess Margaret Hospital (Toronto, Canada), the University of

Stereotactic Radiation Therapy, continued

Colorado and Stanford University of colorectal cancer metastases to the liver treated with SRT was recently reported in abstract form. 65 patients were treated, 42% had 2 or more prior chemotherapy regimens. 12-, 18-, and 24- month local control rates were 84%, 84%, and 66%, respectively. Multivariate analysis for overall survival showed an advantage for patients without extrahepatic disease. Local control also correlated with improved survival. Memorial Sloan-Kettering Cancer Center has also published results of 26 patients treated for metastases < 5 cm in size with local control at 1 year of 77% and median survival of 28.6 months. Results of all these series are similar to results of resection or radiofrequency ablation of liver metastases.

A Medical Technology Assessment performed in June 2011 focused on SRS/SRT/SBRT for metastatic lung tumors. One systematic review and 11 peer-reviewed journal articles were found concerning SRT/SBRT's use in treating lung metastases. Most papers included information concerning patient population size, number of metastases treated, radiation dose, and number of fractions. This information is summarized in **Table 3**.

Table 3. Summary of data collected

Paper	# of Patients	# of Metastatic Lesions Treated	Radiation Dose (Gy)	# of Fractions	Survival (%)
Akoi et al.	11	8	54	9	2 yr = 89.5
Fritz et al.	58	31	30		2 yr = 73
Hamamoto et al.	10	12	48	4	2 yr = 86
Hara et al.		48	30	1	2 yr = 41
Inoue et al.	41	≤5			3 yr = 39
Kim et al.	27		50-60	5	5 yr = 89.4
Kim et al.	13	18	39-51	3	3 yr = 64.7
Norihisa et al.	34	15	48-60	4-5	2 yr = 84.3
Okunieff et al.	50	>5	50	10	2 yr = 25
Rusthoven et al.	38	1-3	48-60	3	
Salazar et al.		7	40	4	3 yr = 23
SUM/AVG	**282**	**~151**	**~45**	**~4.8**	**2 yr ~ 62.6 3 yr ~ 42.2**

Currently, there is no protocol delineating the appropriate dose and fractions needed to treat lung metastases. However, this is not uncommon among stereotactic radiotherapies in general. Doses ranged anywhere from 30−60 Gy with fractions anywhere from 1−10 fractions. As an example, Kim et al. (2010) noted that in hypofractionated stereotactic radiotherapy for primary or metastatic lung cancers, smaller tumor size was a significant prognostic factor for higher local control. Higher radiation doses than 50 Gy/5 fractions were needed in tumors greater than or equal to 2.5 cm for local tumor control. This contrasts with Fritz et al., who published that non-fractionated single-dose irradiation of metastases in the lungs or of small, peripheral bronchial carcinomas is an effective and safe form of local treatment. This could potentially be an issue, as metastatic lung tumors should be clearly differentiated from primary lung cancer and should be given higher doses.

Since no comparative studies exist that compare SBRT to surgical resection of lung metastases, it is difficult to measure the effectiveness of one therapy over the other. Survival rates range from 25%−89.5% after 2 years to 23%−64.7% after 3 years. These data need to be carefully considered. It is not possible at this point to give substantial significance to these survival rates; where little or no information is given as to the origin of the secondary lesion and where metastases from one origin may be more radio-resistive or fatal by nature.

With regards to use of stereotactic radiotherapy for re-irradiation of the spine, studies by Hashmi et al. in 2016 and Arjun et al. in 2009 point to appropriateness of use of SBS/SBT for patients who have undergone previous spinal irradiation. In the Hashmi study, 215 members were treated with salvage SBRT. This study demonstrated no cases of myelopathy with a vertebral compression fracture rate of 4.5%. 6- and 12-month survival was noted to 64% and 48%, respectively. The study noted a randomized trial would be necessary to determine the optimal dosing. The Arjun study from 2009 involved re-irradiation of 19 patients with spinal lesions. This study also saw no radiation-induced myelopathy, though there was no difference in overall survival or PFP between salvage re-irradiated versus all other tumors treated.

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In conclusion, the current literature suggests that SBRT is a practical, relatively safe, and effective treatment for patients unable to undergo surgical resection of lung metastases. Current issues with the technology include no standardized radiation dose, no protocol for the number of fractions, and no protocol for metastatic lesions requiring their own specified dose and fraction.

Billing/Coding Information

CPT CODES

77301 Intensity modulated radiotherapy plan, including dose volume histograms for target and critical structure partial tolerance specification

77338 Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan

32701 Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment

77371 Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based

77372 Radiation therapy delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based

77373 Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fraction

77435 Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions

77432 Stereotactic radiation treatment management of cerebral lesion(s) (complete course of treatment consisting of one session.)

61790 Creation of lesion by stereotactic method, percutaneous, by neurolytic agent (e.g., alcohol, thermal, electrical, radiofrequency); gasserian ganglion

61791 Creation of lesion by stereotactic method, percutaneous, by neurolytic agent (e.g., alcohol, thermal, electrical, radiofrequency); trigeminal medullary tract

61796 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion

61797 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)

61798 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial lesion

61799 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)

61800 Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)

63620 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion

63621 Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)

G0339 Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session, or first session of fractionated treatment.

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Stereotactic Radiation Therapy, continued

G0340 Image guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment

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Revision History

Revision Date	Summary of Changes
7/1/23	Reactivated policy; and for Commercial Plan Policy, updated coverage criteria to align with current clinical standards.
11/11/24	For Commercial Plan Policy, removed criterion #2-biv and #6-d, which both listed the following: “Life expectancy is > 6 months” as a requirement.

Select Health

Stereotactic Radiation Therapy, continued

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MEDICAL POLICY

THERAPEUTIC RADIOPHARMACEUTICALS

Policy # 669
Implementation Date:7/1/23
Review Dates: 5/25/23, 12/5/24
Revision Dates:

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Radiopharmaceutical therapy (RPT) involves the targeted delivery of radiation to tumor cells or to the tumor microenvironment. This treatment approach is distinguished from external beam radiotherapy and brachytherapy in that the radiation is delivered by unencapsulated radionuclides. RPT agents are systemically (in some cases, also locally) administered and localize to the tumor or its microenvironment. Tumor localization may occur because the radioactive element is involved in relevant tumor-associated biological processes or because the radionuclide is conjugated to a delivery vehicle that confers tumor targeting. Alternatively, passive accumulation due to physiologic mechanisms (e.g., enhanced permeability and retention) may provide targeting.

Delivery vehicles that have been investigated include, microspheres, nanoparticles, antibodies, peptides, small molecules, and various constructs of each of these. RPT provides the advantage of beta and Auger electron as well as alpha-particle delivery directly to the targeted cell population. The principal drawback to RPT is that delivery cannot be externally controlled in the way that external beam radiotherapy and brachytherapy may be controlled.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers the following categories of therapeutic radiopharmaceuticals when criteria are met for each:

A. Bone Metastases

1. Strontium 89

A single dose of strontium 89 is considered medically necessary for symptomatic bone metastases when both of the following conditions are met:

a) Confirmed osteoblastic bone metastases from solid organ cancer; and

b) Pain not adequately controlled by conventional therapy.

Strontium 89 is considered not medically necessary when the above criteria are not met, and for all other indications.

B. Lymphoma

1. Ibritumomab tiuxetan (Zevalin

Therapeutic Radiopharmaceuticals, continued

A single course of ibritumomab tiuxetan (Zevalin) is considered medically necessary when any of the following conditions are met:

a) Follicular B-cell CD20 positive non-Hodgkin lymphoma when all the following conditions are met:

i. Individual is age 18 years or older; and

ii. Relapsed or refractory disease, or after initial therapy when individual demonstrates a partial or complete response; and

iii. Individual has adequate marrow reserve (cellularity > 15%, < 25% involvement of lymphoma, and platelets > 100,000 109/L).

a) Other low-grade B-cell CD20 positive non-Hodgkin lymphoma (such as marginal zone or MALT lymphoma) when all the following conditions are met:

i. Individual is age 18 years or older; and

ii. Relapsed or refractory disease; and

iii. Individual has adequate marrow reserve (cellularity > 15%, < 25% involvement of lymphoma, and platelets > 100,000 109/L).

b) For all other conditions, Ibritumomab tiuxetan (Zevalin) is considered experimental/investigational.

C. Neuroendocrine Cancer

1. Lutetium Lu 177 dotatate (Lutathera)

A single course of up to 4 planned injections of Lutetium Lu 177 dotatate (Lutathera) is considered medically necessary for treatment of either of the following:

a) Locally advanced, inoperable or metastatic well-differentiated somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NET), including foregut, midgut and hindgut neuroendocrine tumors in adults

OR

b) Locally advanced or metastatic bronchopulmonary and thymic neuroendocrine tumors when all the following conditions are met:

i. Individual is age 18 years or older; and

ii. An appropriate imaging study has been performed to document somatostatin receptor overexpression; and

iii. Disease has progressed on at least 4 months of somatostatin receptor analog therapy and documented by radiographic imaging; and

iv. Individual has an ECOG performance status of 0-2; and

v. Individual has not had prior treatment with a radiolabeled somatostatin analog.

2. Lutetium Lu 177 dotatate (Lutathera) is considered not medically necessary when:

a) The above criteria are not met and for all other indications

b) Given as a repeat course of treatment (Note: A course can include up to 4 planned injections)

D. Pheochromocytoma and Paraganglioma

1. 131I iobenguane (Azedra)

A single course of 131I iobenguane (Azedra) is considered medically necessary for treatment of adult and pediatric patients 12 years and older with pheochromocytoma or paraganglioma who require systemic anticancer therapy when all the following conditions are met:

a) Individual is age 12 years or older; and

b) Iobenguane scan-positive; and

c) Individual has an ECOG performance status of 0-2; and

d) Patient has not received prior treatment with a radiolabeled somatostatin analog; and

e) Unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma.

2. 131I iobenguane (Azedra) is considered not medically necessary when:

a) The above criteria are not met

b) Given as a repeat course of treatment

c) Used for any other indication not included above

3. Lutetium 177Lu dotatate

A single course of Lutetium 177Lu dotatate is considered medically necessary for primary treatment of unresectable or metastatic pheochromocytoma or paraganglioma when all the following conditions are met:

a) Individual is age 18 years or older; and

b) An appropriate imaging study has been performed to document somatostatin receptor overexpression; and

c) Individual has an ECOG performance status of 0-2; and

d) Patient has not received prior treatment with a radiolabeled somatostatin analog.

4. Lutetium Lu 177 dotatate (Lutathera) is considered not medically necessary when:

a) The above criteria are not met

b) Given as a repeat course of treatment (Note: A course can include up to 4 planned injections)

c) Used for any other indication not included above

E. Prostate Cancer

1. Lutetium Lu 177 vipivotide tetraxetan (Pluvicto)

A single course of Lutetium Lu 177 vipivotide tetraxetan (Pluvicto), up to six doses given every 6 weeks, is considered medically necessary for treatment of prostate cancer when all the following conditions are met:

a) Individual is age 18 or older; and

b) Individual has castrate-resistant, metastatic prostate cancer; and

c) Prostate-specific membrane antigen (PSMA)-positive disease demonstrated by a positive PSMA-11 based PET scan; and

d) Previous treatment with taxane-based chemotherapy; and

e) Previous treatment with ONE of the following androgen receptor (AR) pathway inhibitors:

i. Abiaterone

ii. Apalutamide

iii. Enzalutamide

iv. Darolutamide

2. Lutetium Lu 177 vipivotide tetraxetan (Pluvicto) is considered not medically necessary when:
   a) The above criteria are not met and for all other indications
3. Radium 223 (Xofigo)

A single course of Radium 223 (Xofigo) as monotherapy, up to 6 planned monthly injections, is considered medically necessary for treatment of prostate cancer when all the following conditions are met:

a) Individual is age 18 years or older
b) Individual has a good performance status (ECOG 0-2)
c) Metastatic, castrate-resistant prostate cancer
d) Serum testosterone level is less than 50 ng/dl
e) Disease is worsening or progressing and any of the following conditions are met:
   i. Based on imaging demonstrating worsening bone metastases
   ii. Based on PSA over 5 ng/mL and rising over 2 consecutive lab evaluations

4. Radium 223 (Xofigo) is considered not medically necessary when:
   a) The above criteria are not met and for all other indications
   b) Given as a repeat course of treatment
   c) Systemic radiotherapy with radioisotopes given within the previous 24 weeks
   d) Chemotherapy or biologic therapy given within the previous 4 weeks
   e) Used concurrently with docetaxel or any other systemic therapy except androgen deprivation therapy (ADT)
   f) Used in combination with abiraterone acetate (Zytiga) plus prednisone or prednisolone
   g) There is evidence of spinal cord compression

F. Thyroid Cancer

1. Radioactive iodine 131 is considered medically necessary for differentiated thyroid cancer when any of the following conditions are met:
   a) Definitive treatment for low-risk patients when surgery is not planned (e.g., due to patient comorbidities or refusal)
   b) Adjuvant treatment after total thyroidectomy/partial thyroidectomy (except in low-risk patients)
   c) Treatment of unresectable gross residual disease after total thyroidectomy/partial thyroidectomy
   d) Treatment of known or suspected metastatic disease and radioiodine-avid thyroid scintigraphy
   e) Treatment of persistent disease found on post radioactive iodine therapy imaging
   f) Treatment of suspected recurrence based on biochemical testing
2. Radioactive iodine 131 is considered not medically necessary when the above criteria are not met and for all other indications.

Note: Repeat I-131 should be limited to patients with prior response to radioactive iodine treatment. Repeat treatment should not occur sooner than 6 to 12 months following prior treatment.

Therapeutic Radiopharmaceuticals, continued

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Billing/Coding Information

CPT CODES

A9543 Yttrium Y-90 ibritumomab tiuxetan, therapeutic, per treatment dose, up to 40 millicuries

79403 Radiopharmaceutical therapy, radiolabeled monoclonal antibody by intravenous infusion

A9590 Iodine i-131, iobenguane, 1 millicurie

A9513 Lutetium lu 177, dotatate, therapeutic, 1 millicurie

79101 Radiopharmaceutical therapy, by intravenous administration

A9607 Lutetium lu 177 vipivotide tetraxetan, therapeutic, 1 millicurie

79101 Radiopharmaceutical therapy, by intravenous administration

A9606 Radium ra-223 dichloride, therapeutic, per microcurie

79101 Radiopharmaceutical therapy, by intravenous administration

A9528 Iodine i-131 sodium iodide capsule(s), diagnostic, per millicurie

A9531 Iodine i-131 sodium iodide, diagnostic, per microcurie (up to 100 microcuries)

78012 Thyroid uptake, single/multiple quantitative measurement(s)

78013 Thyroid imaging with vascular flow

78014 Thyroid uptake w/blood flow, single/multiple quantitative measurement(s)

78015 Thyroid carcinoma metastases imaging, limited area

78016 Thyroid carcinoma metastases imaging, additional study

78018 Thyroid carcinoma metastases imaging whole body

A9600 Strontium sr-89 chloride, therapeutic, per millicurie

77750 Infusion or instillation of radioelement solution (includes 3-month follow-up care)

Key References

1. https://www.drugs.com/pluvicto.html
2. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer
3. Sgouros, G. Radiopharmaceutical Therapy. *Health Phys*. 2019 Feb; 116(2): 175–178. doi:10.1097/HP.0000000000001000

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Therapeutic Radiopharmaceuticals, continued

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The codes for treatments and procedures applicable to this policy are included for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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MEDICAL POLICY

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE)

Policy # 349

Implementation Date:7/98

Review Dates: 1/4/00, 2/22/01, 8/15/02, 10/23/03, 11/18/04, 11/7/05, 8/23/07, 8/21/08, 8/13/09, 8/19/10, 9/15/11, 11/29/12, 12/19/13, 12/18/14, 12/10/15, 12/15/16, 12/21/17, 12/13/18, 2/17/20, 2/18/21, 1/4/22, 2/16/23, 1/30/24, 2/19/25

Revision Dates: 8/19/02, 9/14/06, 2/24/25

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Transcatheter arterial chemoembolization (TACE) involves the injection of chemotherapeutic drugs and embolizing agents into the branch of the hepatic artery supplying a tumor. The goal of this procedure is to deliver the chemotherapeutic agents directly to the tumor and to block blood flow to the tumor.

Transcatheter arterial chemoembolization is performed with the intention of reducing the size and/or growth rate of hepatocellular carcinoma. Transcatheter arterial chemoembolization is purported to increase survival length and quality of life due to the resulting decreased tumor burden. In addition, TACE has been proposed for use as a palliative treatment of symptoms associated with functioning neuroendocrine tumors involving the liver. Finally, in a small subset of patients with metastatic disease, TACE may be used to treat specific symptoms related to tumor bulk (e.g., pain).

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers transcatheter arterial embolization (TACE) *in limited clinical circumstances*. It has been proven to improve the health benefit of patients as outlined below.

Covered conditions for TACE include:

1. a) As palliative treatment for patients with neuroendocrine tumors (e.g., carcinoid tumors, pancreatic islet cell tumors) with hepatic metastases when systemic therapy has failed to control symptoms such as carcinoid syndrome (e.g., debilitating flushing, wheezing, and diarrhea), symptoms from non-carcinoid neuroendocrine tumors (e.g., hypoglycemia, severe diabetes, Zollinger-Ellison Syndrome), or symptoms due to hepatic tumor bulk (e.g., pain); or

   b) As palliative treatment for patients with hepatic metastases from colon cancer.
2. As a primary treatment for surgically unresectable primary hepatocellular carcinoma (HCC) when all the following criteria have been met:
   a) The patient has preserved liver function defined as Childs-Turcotte-Pugh class A or B
   b) The patient has 3 or fewer encapsulated nodules that are less than 4 cm in diameter
   c) The patient has no evidence of extra-hepatic metastases
   d) The patient has no evidence of severe renal function impairment
   e) The patient has no evidence of portal hypertension

Select Health

Transcatheter Arterial Chemoembolization (TACE), continued

3. As a palliative treatment for hepatocellular carcinoma when there are significant symptoms related to tumor bulk (e.g., pain)
4. As a palliative treatment for symptoms related to tumor bulk (e.g., pain)

Select Health does NOT cover any other use of TACE therapy. This meets the plan's definition of experimental/investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

For patients with hepatic metastasis from neuroendocrine tumors, the data confirms that chemoembolization does have a role in the palliative care of patients with various neuroendocrine tumor symptoms such as carcinoid syndrome (e.g., severe flushing, wheezing, and diarrhea), Zollinger-Ellison syndrome (multiple bleeding gastrointestinal ulcers), hypoglycemia, severe diabetes, and other neuroendocrine-related manifestations. The treatment has been shown to be useful in significantly diminishing the effect of these symptoms on the patient.

Consequently, TACE can produce significant improvements in the quality of life for individuals with neuroendocrine tumors. Transcatheter arterial chemoembolization is also known to improve symptoms attributable to the effect of tumor bulk associated with either primary or metastatic disease (e.g., pain) through shrinkage of tumor size.

Several well-done randomized controlled trials demonstrate a small but significant increase in survival in patients with unresectable hepatic tumors who meet specific selection criteria. Preserved liver function, 3 or fewer encapsulated nodules, which are less than 4 cm in diameter, absence of extra-hepatic metastases, no evidence of severe renal function impairment, and no evidence of portal hypertension, are all important factors in selecting the appropriate patients and are specifically identified in several studies as a key aspect of the success of TACE treatment. The evidence indicates that those patients who do not meet these criteria do not respond adequately to TACE therapy and receive little or no benefit from the treatment. Transcatheter arterial chemoembolization has also been studied for other indications, including large HCC, preoperative shrinkage of resectable HCC, and for tumor types other than HCC and neuroendocrine tumors. The evidence does not demonstrate that TACE results in a significant advantage in quality of life or length of survival for these conditions. The evidence supporting this conclusion includes non-randomized controlled trials.

Billing/Coding Information

Covered: For the conditions outlined above

CPT CODES

37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction

Select Health

Transcatheter Arterial Chemoembolization (TACE), continued

75894 Transcatheter therapy, embolization, any method, radiological supervision and interpretation

HCPCS CODES

No specific codes identified

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Revision History

Revision Date	Summary of Changes
2/4/25	For Commercial Plan Policy, added coverage criterion #1-B as a qualifying option for this

Select Health

Transcatheter Arterial Chemoembolization (TACE), continued

	treatment: “As palliative treatment for patients with hepatic metastases from colon cancer.”

Select Health

Select Health

MEDICAL POLICY

TUMOR CHEMOSENSITIVITY TESTING

Policy # 470
Implementation Date:12/13/10
Review Dates: 12/15/11, 7/18/13, 8/28/14, 8/20/15, 8/25/16, 8/17/17, 9/18/18, 8/8/19, 8/20/20, 8/19/21, 7/21/22, 8/16/23, 8/15/24
Revision Dates:

Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Chemotherapy is the general term for any treatment involving the use of chemical agents to stop cancer cells from growing. More than half of all people diagnosed with cancer receive chemotherapy. It has been argued that sequential use of active single agents might be preferable to initial combination chemotherapy.

Combination chemotherapy has developed both empirically and through the application of principles and predictions of cancer cell kinetics and drug resistance. The principles for combination chemotherapy regimens include that all drugs must be active as single agents, drug doses should be individually titrated to end-organ toxicity in individual patients, drugs should be chosen for different or synergistic mechanisms of action, drugs should be chosen for non-overlapping toxicity, and drugs should be chosen that have different mechanisms or patterns of resistance.

As an alternative to empiric or experiential selection of chemotherapeutic agents, chemosensitivity assays have been developed. These ex vivo assays are intended to predict the sensitivity of various tumors to chemotherapeutic agents, with the intent of identifying more effective treatment protocols, which would then translate into improved clinical survival. A commercially available assay, the ChemoFx® Assay (Precision Therapeutics, Inc., Pittsburgh, PA), is a decision support tool that measures a specific patient's tumor response to various types, combinations, and doses of chemotherapy selected by the patient's physician. The laboratory test examines how many cancer cells are killed after exposure to treatment, using a patient's living cancer cells that have been removed during a biopsy, aspiration, or surgical procedure. ChemoFx can be used in primary, recurrent, and metastatic tumors.

The assay is an ex vivo assay designed to predict the sensitivity and resistance of a given patient's solid tumor to a variety of chemotherapy agents. A portion of a patient's solid tumor, as small as a core biopsy, is examined. Cultures are exposed to increasing doses of selected chemotherapeutic agents. The number of live cells remaining post-treatment is enumerated microscopically using automated cell-counting software. The resultant cell counts in treated wells are compared with those in untreated control wells to generate a dose-response curve for each chemotherapeutic agent tested on a given patient specimen. Features of each dose-response curve are used to score a tumor's response to each ex vivo treatment as "responsive," "intermediate response," or "non-responsive." Collectively, these scores are used to assist an oncologist in making treatment decisions.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Select Health does NOT cover tumor chemosensitivity testing, including the ChemoFx assay. The limited data on survival improvement, the lack of randomized studies, and the lack of clinical utility of this testing meets the plan's definition of experimental/investigational.

Select Health

Tumor Chemosensitivity Testing, continued

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the Select Health Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

The first published paper on chemosensitivity appeared in the New England Journal of Medicine in 1978. Despite this, there are no current systematic reviews or randomized prospective studies evaluating the role of chemosensitivity testing.

The review by Samson et al. evaluating 10 studies prior to 2004 for chemosensitivity testing showed higher response rates for assay guided therapy but the studies were small and there was limited evidence with regards to survival.

Similar findings are apparent from current literature. In 2010, Herzog et al. reported findings in 192 patients with ovarian cancer. Using ChemoFx and listing the sensitivity as responsive, intermediately responsive, and non-responsive to chemotherapy, the results showed improved survival. Responsive patients had a median survival of 72.5 months and 28.2 months for non-responsive patients toward platinum chemotherapeutic agents.

Another study by Yoshimasu et al. in 2009, evaluated chemosensitivity testing for unresectable, non-small cell lung cancer. In this study, 22 patients had ChemoFx performed to demonstrate effectiveness of gefitinib. Limited outcome data was available and comparison with EGFR copy number and mutation of EGFR was not available.

In summary, limited data is available on survival of patients utilizing chemosensitivity testing and prospective studies have not been performed. Thus, clinical utility remains questionable for this technology in routine clinical practice.

Billing/Coding Information

Not covered: Experimental/investigational/unproven for this indication

CPT CODES

81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
81535	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination
81536	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure)
0083U	Oncology, response to chemotherapy drugs using motility contrast tomography, fresh or frozen tissue, reported as likelihood of sensitivity or resistance to drugs or drug combinations

Select Health

Tumor Chemosensitivity Testing, continued

86849	Unlisted immunology procedure
89240	Unlisted miscellaneous pathology test

HCPCS CODES

No specific codes identified

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Select Health

Tumor Chemosensitivity Testing, continued

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