Getting our priorities straight:
a novel framework for stakeholder-informed prioritization of cancer genomics research

Appendix 1: Candidate Technologies Target Test Profiles and Background Briefs

Test Purpose: Disease Prognosis and Identification of Patients with Poor Outcomes

<table>
<tr><th>Criteria</th><th>Profile</th></tr>
<tr><td>Indication – Population Impact</td><td>• 148,410 new cases each year; 49,960 deaths
• The 5-year survival rate distant colorectal cancer is 24%[1]
• Proportion of population with BRAF mutations is ~10%[2]</td></tr>
<tr><td>Current Standard of Care</td><td>Combinations of 5-FU/Capacitabine/Oxaliplatin/Irinotecan
Bevacizumab/Cetuximab/Panitumumab
NCCN Guidelines: BRAF mutation testing considered but not standard.</td></tr>
<tr><td>Strength of Association
(Clinical Validity)</td><td>• Overall survival for patients with BRAF mutation vs. no BRAF mutations was 15 months (n=17) vs. 24.6 months (n=243), p=0.002, (on standard therapy (capecitabine, oxaliplatin, and bevacizumab). BRAF mutation patients also did worse when cetuximab was added to standard therapy, 15.2 months (n=28) vs. 21.5 months (n=231), p=0.002, for no BRAF mutations. BRAF mutation status is therefore prognostic for a reduction in overall survival.[2]
• In a prospective tumor study (n=1,404), in tumors with a low degree of microsatellite instability, BRAF mutations (n=103), were prognostic for a reduction in overall survival (HR=2.2 [1.4-3.4]).[3]
• In a retrospective tumor analysis, 5 tumors out of 110 tested positive for BRAF mutations, and exhibited significantly lowered overall survival compared to those without BRAF mutations, with an HR of 6.6 [2.4-18.2, p=<0.001].[4]</td></tr>
<tr><td>Potential Clinical Benefits
(Compared to current standard of care)</td><td>
<table>
<tr><th>Test Result</th><th>Potential Benefit</th><th>Population Impacted</th></tr>
<tr><td>BRAF Mutation +</td><td>Prediction of poor outcome Early direction to clinical trials / aggressive chemotherapy</td><td>10% of colorectal cancer patients</td></tr>
<tr><td>BRAF Mutation -</td><td>Prediction of better outcomes Therapeutic regimes with lower toxicities and AEs.</td><td>90% of colorectal patients</td></tr>
</table>
</td></tr>
<tr><td>Potential Clinical Harms
(Compared to current standard of care)</td><td>
<table>
<tr><th>Test Result</th><th>Potential Harm</th><th>Population Impacted</th></tr>
<tr><td>BRAF Mutation +</td><td>AEs of experimental / aggressive chemotherapy</td><td>10% of colorectal cancer patients</td></tr>
<tr><td>BRAF Mutation -</td><td>None, since no change in treatment</td><td>90% of colorectal cancer patients</td></tr>
</table>
All Cases: Misclassification due to genetic testing errors
</td></tr>
<tr><td>Economic Impacts
Cost of therapies
Cost of test</td><td>Cetuximab cost = $2900/week. Total cost (6.1 months[5]) = $33,500
Panitumumab cost ~$3,000/week. Total cost (6 months [6]) = $35,700
BRAF test cost ~ $300</td></tr>
<tr><td>Evidence of Need
Likelihood evidence will change practice</td><td>• Ongoing study by MRC to evaluate tumor testing using BRAF + other genetic markers (Phase II and III, est. completion Aug 2010, n=3240).
• NCCN guidelines recommend using BRAF testing if KRAS is non-mutated</td></tr>
<tr><td>Clinical Trial Implementation and Feasibility</td><td>Relatively low proportion of tumors with BRAF mutations would imply a need for larger sample sizes to detect differences in treatment response.</td></tr>
<tr><td>Market Factors
Clearly defined and consistent coverage position</td><td>No Medicare national or local coverage decision for BRAF mutation testing. No information found at Regence, Anthem, BlueCross BlueShield of Tennessee, Cigna, and Aetna.</td></tr>
</table>

References

1. Guyot F, Faivre J, Manfredi S, Meny B, Bonithon-Kopp C, et al. (2005) Time trends in the treatment and survival of recurrences from colorectal cancer. Ann Oncol 16: 756-761.

2. Tol J, Nagtegaal ID, Punt CJ (2009) BRAF mutation in metastatic colorectal cancer. N Engl J Med 361: 98-99.

3. Roth AD, Tejpar S, Delorenzi M, Yan P, Fiocca R, et al. (2010) Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 28: 466-474.

4. Laurent-Puig P, Cayre A, Manceau G, Buc E, Bachet JB, et al. (2009) Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol 27: 5924-5930.

5. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, et al. (2007) Cetuximab for the treatment of colorectal cancer. N Engl J Med 357: 2040-2048.

6. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, et al. (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 25: 1658-1664.

CANCERGEN Topic Brief

BRAF Mutation Testing in Colorectal Cancer to Guide Use of Cetuximab and Panitumumab

Test Purpose: Disease prognosis and Identification of Patients with poor outcomes

Indication – Population Impact

Colorectal cancer (CRC) is the 3rd most commonly-diagnosed cancer, and third highest cause of cancer death in the United States. The American Cancer Society estimated that 148,810 people were diagnosed with colorectal cancer in 2008, and 49,960 people would die from the disease. 5-year relative survival rates are around 36% for local recurrence and 24.0% for distant metastases[1].

The BRAF protein is involved in sending signals in cells and in cell growth, and specific mutations in the gene may be prognostic for disease prognosis or predictive for treatment response in advanced colorectal cancer. Approximately 10% of the colorectal tumors test positive for BRAF mutations.

Current Standard of Care

The current standard of care for metastatic colon cancer includes cytotoxic agents such as 5-FU, irrinotecan, and capecitabine. Platinum-based agents such as oxaliplatin and the VEGF monoclonal antibody bevicizumab are also used, and the exact combination depends upon clinical factors, and patient/oncologist preferences.[2] The anti-Epidermal Growth Factor Receptor (EGFR) antibodies cetuximab and panitumumab are also approved for CRC treatment.[3]

Cetuximab in combination with irinotecan vs. cetuximab alone was compared in a RCT in which a majority of patients were EGFR IHC+. The median time to progression was significantly longer for patients receiving combination therapy (4.1 vs. 1.5 months).[4] In another RCT, comparing cetuximab to best palliative care (n=572), patients previously treated with fluoropyrimidine, irinotecan, and oxaliplatin or with contraindications to these drugs, and IHC+ for EGFR, who were randomized to cetuximab demonstrated a statistically significant improvement in overall survival (OS) compared to those randomized to best supportive care (median OS: 6.1 vs. 4.6 months; HR=0.766, p=0.0048).[5] Side effects included rash in the cetuximab group 11.8% vs. 0.4% in best supportive care group, infection without neutropenia (12.8% vs. 5.5%), confusion (5.6% vs. 2.2%), and pain defined as “other” (14.9% vs. 7.3%).

Panitumumab was evaluated in an RCT randomizing patients (n=463) to either best supportive care (BSC) or BSC + panitumumab. The mean progression-free survival was 96 days for patients receiving panitumumab and 60 days for patients receiving BSC alone (HR=0.54 [0.44-0.66]). However, the median times to progression were similar (~ 8 weeks). There were no differences in overall survival between groups. Side effects (Grade 3+) in the panitumumab group included erythema 5% vs. 0% in BSC, dermatitis acneform 7% vs. 0% in BSC, and abdominal pain (7%) vs. 4% in BSC.[6]

NCCN guidelines indicate testing for KRAS mutations in the initial workup for suspected colorectal cancer. If KRAS is non-mutated, BRAF testing should be consideration. NCCN guidelines state: “Patients with a known BRAF mutation appear unlikely to benefit from anti-EGFR antibodies…”, i.e. cetuximab and panitumumab.”

Strength of Genomic Association – Clinical Validity

BRAF mutations have been associated with poorer disease prognosis and decreased treatment response to anti-EGFR antibodies.[7] In the CAIRO2 trial, patients with metastatic colorectal cancer were randomized to either standard treatment (capecitabine, oxaliplatin, and bevacizumab), or to standard treatment + cetuximab. In the trial, overall there was no difference in overall survival between the treatment groups (20.3 months vs. 19.4 months, p=0.16). Subgroup results based on BRAF status are shown in the table below. BRAF was associated with poorer outcomes for both treatment arms. There did not appear to be a significant difference in response to cetuximab based on BRAF status.

CAIRO2 Trial; Metastatic Colorectal Cancer, Median Overall Survival[7]			
	Median Overall Survival		
	Capecitabine, oxaliplatin, and bevacizumab + cetuximab	Capecitabine, oxaliplatin, and bevacizumab	Hazard Ratio
BRAF Mutation +	15.2 months (n=28)	15.0 months (n=17)	n/a
BRAF Mutation –	21.5 months (n=231)	24.6 months (n=243)	n/a
	P= 0.002 (no HR values reported)	P= 0.002 (no HR values reported)	

In another recent study, out of 110 tumor samples collected retrospectively in patients treated with cetuximab as a 2nd line or later therapy, 5 tumors tested positive for BRAF mutations. These patients exhibited significantly lowered overall survival compared to those without BRAF mutations, with an HR of 6.6 [2.4-18.2, p=<0.001].[8]

Retrospective Tumor Analysis of Patients with Metastatic CRC [8]. Patients treated with cetuximab-based regimen as 2nd line+ therapy	
	Median Overall Survival
BRAF Mutation + (n=5)	6.5 months
BRAF Mutation – (n=110)	14.8 months
	HR= 6.6 [2.4-18.2], p<0.001

Leveraging the PETACC-3 adjuvant trial (Stage II to III colon cancer), Roth et al. conducted a prospective collection and DNA extraction from tumor samples (n=1,404), and examined the impact of BRAF mutations. They found that in tumors with a low degree of microsatellite instability (MSI <3), BRAF mutations (n=103), were prognostic for a reduction in overall survival (HR=2.2 [1.4-3.4, p=0.0003). The number of events was considered too small to obtain reliable information from the MSI 3+ group.[9]

Prospect Tumor Analysis of Patients with Metastatic CRC, Standard Therapeutic Regimens, MSI <3 [9]	
	Median Overall Survival
BRAF Mutation + (n=103)	Undetermined (75% survival = 3 years)
BRAF Mutation – (n=1,204)	Undetermined (75% survival = 6 years)
	HR= 2.2 [1.4-3.4], p=0.0003

In summary, patients with BRAF mutations appear to have significantly poorer disease prognosis; the data do not support differential response to cetuximab in particular. There are no treatments that have been shown to improve survival specifically for patients with BRAF mutation.

Potential Benefits

The most immediate and obvious benefit of BRAF testing, as suggested by the NCCN guidelines, is to avoid anti-EGFR antibody therapy in patients who are unlikely to benefit, thus avoiding unnecessary treatment toxicities. Beyond this immediate implication, BRAF mutation positive patients could either be directed to clinical trials for experimental treatments, or aggressive chemotherapeutic regimes, which may offer these patients improved survival outcomes.

Potential Harms

BRAF mutation positive patients may experience the side effects of experimental therapies and/or more aggressive chemotherapy regimes. BRAF mutation negative patients do not experience any difference since the standard of care remains the same. However, in addition to the above, tests are imperfect and there is a risk that patients may be misclassified and receive unintended treatment.

Economic Impact

The BRAF genetic test is estimated to cost approximately $300[10]. Treatment with cetuximab requires an initial loading dose of 400 mg/m^2 followed by a weekly maintenance dose of 250 mg/m^2. This leads to a cost of approximately $2874 for the initial loading dose and a cost of $1796 for each weekly maintenance dosage. Assuming an overall survival of 6.1 months [5], the total cost of treatment is estimated to be ~$33,500.

Panitumumab allows for the option of being administered in doses of 2.5 mg/kg/week, 6 mg/kg every 14 days or 9mg/kg every 21 days as a form of maintenance therapy [9]. There is a cost of approximately $2976 for each 2 week treatment regimen per patient associated with using panitumumab, and no

initial loading dose is required. Assuming a median overall survival of 6 months [6], the cost of panitumumab treatment is estimated to be ~$35,700.

Evidence of Need

One on-going study being conducted by the Medical Research Council in the UK looks at tumor testing using KRAS, BRAF and Topo-1 in patients with metastatic or locally advanced colorectal cancer. This two-part study consists of a phase II and phase III component and has an estimated enrollment of 3240 subjects. Part I of the study feasibility of testing (patient participation, reproducibility of results, and real costs) while part II stratifies patients into four groups – KRAS mutation, BRAF mutation and Topo-1 expression – and investigate each group's response rate to specific treatments. The estimated completion date is August 2010[11].

A small ongoing clinical trial being conducted by Velje Hospital in Denmark is investigating the effect of preoperative combination chemotherapy in patients with locally advanced colon cancer with mutation in BRAF in comparison to chemotherapy in combination with panitumumab in patients without BRAF mutations. Estimated enrollment in the study is low, with only 66 subjects. The primary outcome is the frequency of patients requiring adjuvant chemotherapy based on histological evaluation from surgery while the secondary outcomes look at recurrence free survival and overall survival. This is a phase II clinical trial and is expected to be completed by July 2011[12].

Another small study currently being conducted by Leiden University Medical Center is studying how well simvastatin given together with panitumumab works in treating patients with advanced or metastatic colorectal cancer. The primary objective looks at the PFS rate at 11 weeks after the first dose of panitumumab while one of the multiple tertiary (exploratory) objectives looks at the correlation of PTEN, PIK3CA, BRAF, ERL and MEK status and response rate. Again, study enrollment is low with 46 patients. This is also a phase II clinical trial and the estimated primary completion date is April 2012[13].

In summary, although there is a lack of clear evidence on the impact of BRAF testing for colorectal cancer, NCCN guidelines suggest consideration of BRAF testing to guide cetuximab use, and only several small studies appear to be evaluating this issue.

Clinical Trial Implementation and Feasibility

No particular challenges to conducting a study in this area are obvious, although the relatively low proportion of tumors with BRAF mutations would imply a need for larger sample sizes to detect differences in treatment response.

Market Factors

A review of medical/clinical policies at Regence, Anthem, BlueCross BlueShield, Cigna, Aetna, and Medicare found no information related to BRAF mutation testing. No Medicare national or local coverage decision was located.

References

1. Guyot F, Faivre J, Manfredi S, Meny B, Bonithon-Kopp C, et al. (2005) Time trends in the treatment and survival of recurrences from colorectal cancer. Ann Oncol 16: 756-761.

2. NCCN (2010) NCCN Guidelines on Colon Cancer.

3. NCI (2007) FDA Approval for Cetuximab. In: FDA, editor.

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8. Laurent-Puig P, Cayre A, Manceau G, Buc E, Bachet JB, et al. (2009) Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol 27: 5924-5930.

9. Roth AD, Tejpar S, Delorenzi M, Yan P, Fiocca R, et al. (2010) Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. J Clin Oncol 28: 466-474.

10. http://www.ohsu.edu/pathology/TransResLabCut_Mel.php (2010) Cutaneous Melanoma - BRAF and NRAS genes.

EGFR Mutation Testing for Erlotinib Maintenance Therapy after 1st Line Chemotherapy in Non-Small Cell Lung Cancer (NSCLC)

Test Purpose: Prediction of Patients most likely to benefit with Erlotinib maintenance therapy

<table>
<tr><th>Criteria</th><th>Profile</th></tr>
<tr><td>Indication – Population Impact</td><td>Lung Cancer Stage IIIA+
196,454 New Cases / 158,599 Deaths[1].
80% lung cancers are NSCLC[2]
10% of NSCLC tumors are EGFR mutation positive[3].</td></tr>
<tr><td>Current Standard of Care</td><td>After successful 1st-line treatment: observation, erlotinib, or pemetrexed</td></tr>
<tr><td>Strength of Association
(Clinical Validity)</td><td>
<table>
<tr><th colspan="4">SATURN Trial – Erlotinib vs. Placebo for Maintenance Therapy [4]</th></tr>
<tr><th>Median PFS</th><th>Erlotinib</th><th>Placebo</th><th>HR p value or 95% CI</th></tr>
<tr><td>EGFR Mutation+</td><td>48 weeks (estimated),n=22</td><td>12 weeks (estimated), n=27</td><td>HR = 0.10; [0.04-0.25]; p < 0.0001</td></tr>
<tr><td>EGFR Mutation -</td><td>13 weeks (estimated), n=199</td><td>12 weeks (estimated),n=189</td><td>HR = 0.78; [0.63-0.96] p<0.0185</td></tr>
<tr><td>All patients</td><td>12.3 weeks</td><td>11.1 weeks</td><td>HR=0.69; [0.62-0.82] p<0.0001</td></tr>
</table>
</td></tr>
<tr><td>Potential Clinical Benefits
(Compared to current standard of care)</td><td>
<table>
<tr><th>Standard Care</th><th>Potential Benefit</th><th>Population impacted</th></tr>
<tr><td>Observation</td><td>Patients most likely to respond receive drug</td><td>10% of NSCLC patients</td></tr>
<tr><td>Erlotinib Maintenance</td><td>Patients less likely to respond avoid adverse events (AEs)</td><td>90% of NSCLC patients</td></tr>
<tr><td>Pemetrexed Maintenance</td><td>EGFR mutation+ patients avoid pemetrexed AEs, potentially receiving greater benefits.</td><td>10% of NSCLC patients</td></tr>
</table>
</td></tr>
<tr><td>Potential Clinical Harms
(Compared to current standard of care)</td><td>
<table>
<tr><th>Standard of Care</th><th>Potential Harm</th><th>Population impacted/ Grade 3+ AEs</th></tr>
<tr><td>Observation</td><td>Erlotinib AEs for EGFR mutation+ patients</td><td>10% of NSCLC patients / 6% Rash, 2% Diarrhea</td></tr>
<tr><td>Erlotinib Maintenance</td><td>EFGR mutation- patients lose any survival benefit of erlotinib</td><td>90% of NSCLC patients</td></tr>
<tr><td>Pemetrexed Maintenance</td><td>EGFR mutation+ patients avoid unknown benefit of pemetrexed over erlotinib, and suffer erlotinib AEs.</td><td>10% of NSCLC patients unknown survival benefit/ 6% Rash, 2% Diarrhea</td></tr>
</table>
All Cases: Misclassification due to genetic testing errors
</td></tr>
<tr><td>Economic Impacts
Cost of therapies
Cost of test</td><td>Erlotinib cost $472/week
Median duration of treatment for EGFR mutation+ patients ~ 44 weeks ($20,768)
Median duration of treatment for EGFR mutation- patients ~ 14 weeks ($6,608)[5]
Diagnostic Test ($1400)[6]</td></tr>
<tr><td>Evidence of Need
Likelihood evidence will change practice</td><td>Association data based on ~50 mutation (+) patients
Benefit of pemetrexed vs. erlotinib in maintenance setting unclear in EGFR+
No large Phase III RCTs currently underway based on ClinicalTrials.gov</td></tr>
<tr><td>Clinical Trial Implementation and Feasibility</td><td>Depending on trial design, relatively few patients (~10% in U.S.) are EGFR+ and recruitment may be challenging.
Alternatively could evaluate 1st-line setting</td></tr>
</table>

Market Factors Clearly defined and consistent coverage position	Private payers consider EGFR testing in Non Small Cell Lung Cancer to be investigational and therefore not eligible for reimbursement. Medicare does not cover EGFR testing in NSCLC.

References

1. CDC (2010) Lung Cancer Statistics.

2. Jemal A, Siegel R, Ward E, Murray T, Xu J, et al. (2006) Cancer statistics, 2006. CA Cancer J Clin 56: 106-130.

3. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, et al. (2009) SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC. J Clin Oncol (Meeting Abstracts) 27: 8001-.

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CANCERGEN Topic Brief

EGFR Mutation Testing for Erlotinib Maintenance Therapy after 1st Line Chemotherapy in Advanced Non-Small Cell Lung Cancer (NSCLC)

Test Purpose: Prediction of patients most likely to benefit with erlotinib maintenance therapy after 1st line chemotherapy

Indication – Population Impact

Lung Cancer is the most common type of cancer in the US, with a patient burden that is higher than breast, prostate and colon cancer combined.[1] Of the prevalent cases of lung cancer, approximately 56% are advanced stage (Stage IIIB/IV)[2]. Approximately 80% of lung cancers are defined as non-small cell lung cancers (NSCLC).[3] The 5 year survival in advanced stage lung cancer is 3.5%.[2]
Genetic mutations of the EGFR (epidermal growth factor receptor) gene, occurring in about 10% of tumors, have been associated with improved response to treatment with EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib (Tarceva).[4]

Current Standard of Care

For advanced NSCLC (Stage IIIB/IV), first line treatment includes a combination of surgery, radiotherapy and chemotherapy. Chemotherapeutic agents include drugs such as paclitaxel and carboplatin which are often used in combination. After successful treatment with first-line chemotherapy, maintenance therapy with pemetrexed or erlotinib may be prescribed in the absence of disease progression, based upon recent clinical trials.[4,5] In a study of maintenance therapy using pemetrexed, the median PFS for patients on pemetrexed (n=441) was 4.3 months vs. 2.6 months on placebo (n=222), HR=0.5 (0.42-0.61), and the median OS was 13.4 vs. 10.6 months, HR=0.79 (0.65-0.95). Adverse effects (grade 3 or higher) that were significantly greater in pemetrexed than placebo and are listed as follows: fatigue (5% vs. 1%), neutropenia (13% vs. 0%).[5] Pemetrexed is currently approved for maintenance treatment of patients with locally advanced or metastatic non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

Erlotinib is currently approved for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Trial results are shown in the "Strength of Genomic Association" section below.
NCCN guidelines recommend EGFR mutation testing to guide erlotinib therapy in 2nd-line treatment for patients with poor performance status (PS 3-4), or in 1st-line therapy (for which erlotinib does not have an FDA indication).

Strength of Genomic Association – Clinical Validity

The prognostic and predictive effects of EGFR mutations were evaluated in the recent SATURN trial, which compared maintenance erlotinib to placebo (observation). In this study, maintenance therapy significantly improved progression-free survival (hazard ratio [HR], 0.71; median, 12.3 vs 11.1 weeks) and overall survival (HR, 0.81; median, 12.0 vs 11.0 months). Adverse effects (grade 3 or higher) that were significantly greater in erlotinib than placebo and are listed as follows: rash (9% vs. 0%), diarrhea (2% vs. 0%).[6]

SATURN Trial – Erlotinib vs. Placebo for Maintenance Therapy in NSCLC Patients without Disease Progression after 1st line Treatment with Platinum-based Chemotherapy [6]			
Median Progression-free survival (PFS)	**Erlotinib**	**Placebo**	**HR and p value or 95% CI**
EGFR Mutation +	48 weeks (estimated) n=22	12 weeks (estimated), n=27	HR = 0.10; [0.04-0.25]; p < 0.0001
EGFR Mutation -	13 weeks (estimated) n=199	12 weeks (estimated) n=189	HR = 0.78; [0.63-0.96] p<0.0185
All patients	12.3 weeks	11.1 weeks	HR=0.69; [0.62-0.82] p<0.0001

Patients with EGFR mutations (n=22) had a significantly better treatment response on erlotinib than patients without mutations (n=189), and the improvement in patients without an EGFR mutation was smaller but statistically significant.

Potential Benefits

The potential benefits of maintenance erlotinib for EGFR+ mutations vary depending upon the comparator (standard of care), which can be observation, pemetrexed or erlotinib.
If observation is the standard of care, use of erlotinib in patients with EGFR mutations would lead to increased PFS in those patients.

If pemetrexed is the standard of care, patients with EGFR mutations that are prescribed erlotinib, will avoid adverse effects of pemetrexed such as anemia[5], while potentially experiencing the increased benefit of erlotinib vs. pemetrexed, although the relative benefit between erlotinib and pemetrexed is currently unknown.

If erlotinib is the standard of care, than patients not testing positive for tumors with EGFR mutations will (presumably) not be prescribed erlotinib and therefore avoid the moderate side effects associated with erlotinib including grade 3/4 diarrhea(2%) and rash (9%)[4].

Potential Harms

As above, the potential impact of undesirable effects depends upon the standard of care adopted.
If observation is the standard of care, patients with EGFR mutations will be prescribed erlotinib maintenance therapy with the possibility for consequent adverse effects. Patients not testing positive for EGFR mutations will not suffer any side effects.

If pemetrexed is the standard of care, patients testing positive for EGFR mutations in their tumors will be prescribed erlotinib. However, erlotinib vs. pemetrexed in this population have not been directly compared.

If erlotinib is the standard of care, then patients negative for EGFR tumors will not be prescribed erlotinib for maintenance therapy, and therefore not receive any potential benefits.

Economic Impact

Erlotinib has been priced at approximately $470/week[7]. For treatment duration of 44 weeks (EGFR mutation+ subgroup, median PFS), the estimated cost is $20,680. For duration of 14 weeks (EGFR mutation- subgroup, median PFS), the estimated cost is $6,580. The cost of the genetic test is estimated to be approximately $1400[8].

Evidence of Need

The effectiveness of prescribing erlotinib vs. premetrexed in EGFR mutation positive patients is unknown, although in the general population data for each of these treatments vs. placebo are available[4,5]. It should be noted that the EGFR mutation data from the SATURN trial included only ~49 patients. Although lung cancer is the most prevalent form of cancer, only about 10% of these cancers are positive for EGFR mutations.

There are several ongoing clinical trials that can provide information on using erlotinib as a form of maintenance therapy in patient with EGFR mutations. One such study is a phase III clinical trial, being conducted in China, which compares the effectiveness of using erlotinib as maintenance therapy vs. gemcitabine or carboplatin in stage IIIB/IV NSCLC patients. The study will enroll 160 patients and examine the progression free survival as a primary outcome.[8] Another ongoing phase III clinical trial being conducted in France is investigating the effects of administering erlotinib immediately after the end of first-line chemotherapy. It will examine progression free survival as a primary outcome and overall survival as a secondary outcome with 435 patients.[9]

Clinical Trial Implementation and Feasibility

The major challenge in conducting a US-based trial in patients with EGFR mutations is the low prevalence (5-10%). In addition to use of erlotinib as maintenance therapy, 1st-line erlotinib use in patients with EGFR mutations could be evaluated in a clinical trial.

Market Factors

Anthem, Regence, and BlueCross BlueShield of Tennessee consider EGFR testing for NSCLC investigational and, therefore, not covered. The consistency between the three BlueCross plans likely reflects the BlueCross BlueShield Association's position in BCBSA's medical policy, which is not publicly accessible. Many Blues Plan policies will be consistent with the Association's position. BlueCross BlueShield of Tennessee's medical policy manual lists two studies that suggest that the analysis of somatic mutations of the epidermal growth factor receptor gene is "not a competent means of deselecting individuals for erlotinib treatment. Cigna has not addressed EGFR testing for NSCLC in a coverage policy. No national or local coverage decision has been issued by Medicare or its contractors.

Recently, the National Institute for Clinical Excellence (NICE) approved the coverage of gefitnib for non-small cell lung cancer in EGFR mutation positive patients. NICE recommends gefitnib for the first line treatment of advanced or metastatic non-small cell lung cancer only in patients that are EGFR mutation positive.

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ERCC1 Expression Testing for Platinum-Based (Cisplatin/Carboplatin) Adjuvant Therapy in Resected Early-Stage Non-Small Cell Lung Cancer (NSCLC)

Test Purpose: Disease Prognosis and Prediction of Treatment with Chemotherapy

<table>
<tr><th>Criteria</th><th>Profile</th></tr>
<tr><td>Indication – Population Impact</td><td>

~85% NSCLC; 40% Dx early stage (1)(2) out of 219,440 diagnosed (2009)
5-year survival: 23% (Stage IIIA), 67% (Stage IA)
40-50% of tumors are ERCC1 protein expression positive(3)

</td></tr>
<tr><td>Current Standard of Care</td><td>Stage I: Observation; Stage II-III: platinum-based adjuvant chemotherapy
Adjuvant chemotherapy provides an absolute improvement in 5-year survival rates of ~4%. Grade 3 or 4 toxicities consist mainly of fatigue (5.5-23%) and neutropenia (40-65%). No NCCN guidelines for ERCC1 testing.</td></tr>
<tr><td>Strength of Association
(Clinical Validity)</td><td>
<table>
<tr><th>Median OS: IALCT trial(4)</th><th>Adjuvant Chemotherapy</th><th>Observation</th><th></th></tr>
<tr><td>ERCC 1+</td><td>50 (n=165)</td><td>55 (n=170)</td><td>HR = 1.14 (0.84-1.55), p=0.40.</td></tr>
<tr><td>ERCC1-</td><td>56 (n=224)</td><td>42 (n=202)</td><td>HR = 0.65 (0.50 – 0.86), p=0.002</td></tr>
<tr><td></td><td>HR=1.16 (0.86-1.56), p=0.34</td><td>HR=0.66 (0.49-0.90), p=0.009</td><td></td></tr>
</table>

ERCC1 positive: better prognosis untreated
ERCC1 negative: better response to treatment

</td></tr>
<tr><td>Potential Clinical Benefits
(Compared to current standard of care)</td><td>
<table>
<tr><th>Test Result[5]</th><th>Potential Benefit</th><th>Population Impacted</th></tr>
<tr><td>ERCC1 +</td><td>Assigned to non-platinum chemotherapy; improved outcomes, reduced AEs</td><td>~44% NSCLC patients</td></tr>
<tr><td>ERCC1 -</td><td>Early assignment to platinum chemotherapy; improved outcomes</td><td>~56% of NSCLC patients</td></tr>
</table>
</td></tr>
<tr><td>Potential Clinical Harms
(Compared to current standard of care)</td><td>
<table>
<tr><th>Test Result</th><th>Potential Harm</th><th>Population Impacted</th></tr>
<tr><td>ERCC1 +</td><td>Unknown benefit of platinum vs. non-platinum adjuvant therapies</td><td>~44% NSCLC patients</td></tr>
<tr><td>ERCC1 -</td><td>AEs of chemotherapy at earlier stage</td><td>~56% of NSCLC patients</td></tr>
</table>
All Cases: Misclassification due to genetic testing errors, particularly for IHC test
</td></tr>
<tr><td>Economic Impacts
Cost of therapies
Cost of test</td><td>Cisplatin / Carboplatin ~ $5,000 /course.[6]
Average # of courses = 3. Estimated total cost = $15,000
ERCC1 test cost ~ $331[7]</td></tr>
<tr><td>Evidence of Need
Likelihood evidence will change practice</td><td>

Ongoing SWOG phase II trial in Stage I using ERCC1 and RRM1 to select between observation or treatment with cisplatin-gemcitabine (n=55)[8]
French IFCT trial utilizing ERCC1 and EGFR mutation status to direct patient treatment to erlotinib, observation, platinum chemo + erlotinib, and platinum chemo (n=108).[9]

</td></tr>
<tr><td>Clinical Trial Implementation and Feasibility</td><td>No particular challenges to conducting a study in this area are obvious.</td></tr>
</table>

Market Factors Clearly defined and consistent coverage position	No Medicare national or local coverage decision for ERCC1 testing. No information found at Regence, Anthem, BlueCross/BlueShield, Cigna, and Aetna.

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ERCC1 Expression Testing for Platinum-Based (Cisplatin/Carboplatin) Adjuvant Therapy in Resected Early-Stage Non-Small Cell Lung Cancer (NSCLC)

Test Purpose: Disease Prognosis and Prediction of Treatment with Chemotherapy

Indication – Population Impact

Lung Cancer is the leading cause of cancer death in the US, with more men and women dying from lung cancer than breast, colon and prostate cancers combined. In 2009, it is estimated that 116,090 men and 103,350 women were diagnosed with lung cancer and 88,900 men and 70,490 women died from lung cancer (accounting for about 28% of all cancer deaths). Roughly 85-90% of lung cancers are defined as non-small cell lung cancers (NSCLC).[1] The percentage of patients diagnosed with stage I NSCLC is 13.4% while diagnosis at stage II and III are 2.8% and 25% respectively.[2] 5-year survival rates range from 23% for stage IIIA to 67% for stage IA NSCLC is 67%.[3]

ERCC1 (excision repair cross complementation 1) protein expression levels as measured by Immunohistochemistry (IHC) have been shown to provide prognostic information (i.e. impacting the survival of patients independent of treatment) as well as predictive information (i.e. impacting the treatment effect therapy) in resected early stage NSCLC. IHC refers to the process of localizing antigens or proteins in tissue samples by using labeled antibodies as specific reagents through antigen-antibody interactions that are visualized by a marker. Approximately 40-50% of early stage NSCLC patients test ERCC1 protein expression positive.[4]

Current Standard of Care

The use of adjuvant chemotherapy in resected stage I NSCLC is controversial, and observation alone or adjuvant platinum-based chemotherapy are both used in practice depending on clinical factors and patient preference.[5] Platinum-based doublet chemotherapy, using carboplatin or cisplatin, is the standard of care for resected stage II-IIIA NSCLC.[6] The cytotoxic agents used frequently in combination with cisplatin/carboplatin include vinorelbine, gemcitabine, paclitaxel or docetaxel. Adjuvant chemotherapy provides an absolute improvement in 5-year survival rates of ~4%, increasing survival from 60% to 64%.[7] Grade 3/4 toxicities consist mainly of fatigue (5.5-23%) and neutropenia (40-65%).[8,9]

Current NCCN guidelines only note the relationship between using ERCC1 testing in NSCLC, stating that "High levels of ERCC1 expression are also predictive of poor response to platinum-based chemotherapy." No guidelines were identified recommending use of ERCC1 testing.[6]

Strength of Genomic Association –Clinical Validity

Higher ('positive') expression levels of ERCC1 have been associated with significantly better disease prognosis, and lower ('negative') expression levels have been associated with significantly better response to treatment with platinum-based chemotherapy. Specifically, the landmark trial by Olaussen[10] et al published in 2006 compared adjuvant cisplatin based chemotherapy with observation only, in stage I-III NSCLC patients. The study found improved survival for untreated ERCC1-positive patients, and improved treatment response for ERCC negative patients. The role of ERCC1 as a predictor of treatment response was confirmed with a statistically significant interaction test (p=0.009). Thus,

these results imply that patients with lower ERCC1 levels are better candidates for chemotherapy because they have a worse disease prognosis yet respond better to treatment.

Median overall survival (months) from IHC analysis of IALCT trial(7)

	Adjuvant Chemotherapy	Observation	
ERCC 1+	50 (n=165)	55 (n=170)	HR = 1.14 (0.84-1.55), p=0.40.
ERCC1-	56 (n=224)	42 (n=202)	HR = 0.65 (0.50 – 0.86), p=0.002
	HR=1.16 (0.86-1.56), p=0.34	HR=0.66 (0.49-0.90), p=0.009	

A subsequent smaller retrospective study in 45 resected NSCLC patients (stage I-IV) who received adjuvant or neoadjuvant platinum-based chemotherapy found improved survival in ERCC1-negative (vs. ERCC1-positive) patients, with OS (102 weeks vs. 56 weeks) HR = 2.580 (1.17 – 4.08), p=0.014[11]

Retrospective Analysis of 45 patients, resected NSCLC (Stage 1-III), Median OS (weeks)[11]

	Neoadjuvant Chemotherapy
ERCC1+	56 (n=20)
ERCC1-	102 (n=25)
	HR=2.58 (1.17-4.08), p=0.014

Potential Benefits

The potential benefit of ERCC1 expression testing will depend on the stage of NSCLC and the subsequent standard of care comparator.

In Stage I NSCLC, where observation alone may be the standard of care, using an ERCC1 test may help practitioners decide whether or not to use platinum-based chemotherapies for these patients. Patients with ERCC1-positive tumors likely would be observed, while negative patients might choose to receive therapy.

Another potential use of ERCC1 expression testing is for stage II-III NSCLC, where adjuvant platinum-based chemotherapy is the standard of care. In this case, the potential benefit arises from the ability to tailor chemotherapy based on ERCC1 expression status. ERCC1-negative patients would receive the standard platinum-based chemotherapy, while ERCC1-positive patients could receive a non-platinum-based chemotherapy (e.g. gemcitabine).[12] Platinum-based therapies have been associated with statistically significant increases in rates of anemia, neutropenia, thrombocytopia, nausea, vomiting and toxic death when compared with non-platinum based therapies [13]. In the IALT trial, 22.6% of patients experienced at least one grade 4 side effect.[14]

Potential Harms

As above, the potential impact harms depend upon the stage of NSCLC and the subsequent standard of care comparator.

In Stage I NSCLC, if observation is the standard of care, patients with ERCC1-negative expression who are prescribed adjuvant platinum-based chemotherapy will be at risk of serious adverse events.
In Stage II-III, ERCC1-positive expression patients likely would be prescribed a non-platinum based regimen for adjuvant therapy; however there are few studies that have been conducted in patients with early stage non-small cell lung cancer, making it difficult to determine the relative benefits associated with platinum vs. non-platinum care. In advanced stage NSCLC, there are higher toxicities associated with using a platinum based chemotherapy regimen versus gemcitabine, but there is also greater progression-free/overall survival.

In addition to the above, tests are imperfect and there is a risk that patients may be classified and differentially depending on the lab conducting the test (because ERCC1 test is an immunohistochemical test for which standardization is challenging), and receive inappropriate treatment. There has been some controversy in regard to the assays used in the studies above. [15]

Economic Impact

The list price for the ERCC1 analysis in NSCLC is $331.[16] The cost per course of cisplatin is approximately $4858 while the cost per course of carboplatin is approximately $5025.[17] The average number of courses that a patient undergoes is three.[17]

Evidence of Need

The effectiveness and toxicities of prescribing platinum vs. non-platinum-based adjuvant therapy for ERCC1-positive patients is unknown in early-stage NSCLC. Data from late-stage NSCLC indicate an increased response-rate and decreased number of febrile (development of fever) neutropenia events, but no change in progression free survival (PFS), overall survival, or time to progression (TTP) between platinum-based adjuvant therapy regardless of ERCC1 status vs. tailored therapy based on ERCC1 status.[12] Whether these results translate to early-stage NSCLC is unknown.

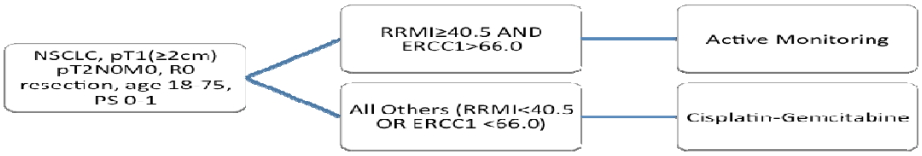
There are several ongoing clinical trials that will provide additional information on this topic (see Figure 1), although they will not fully address the potential role of ERCC1 in early stage NSCLC for several reasons, as described below.

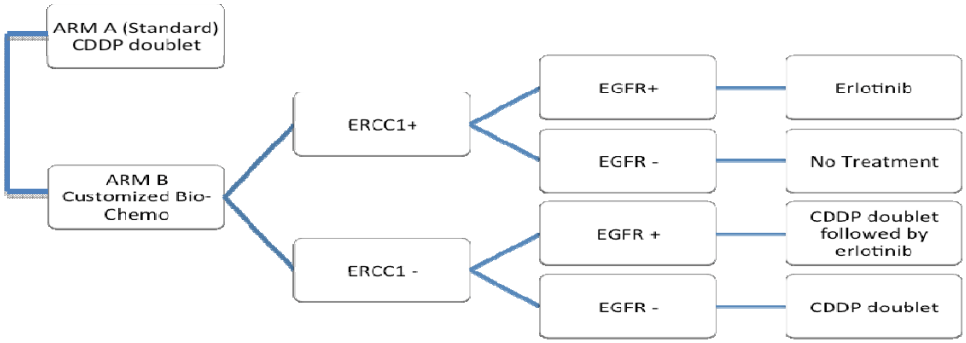
In a phase II study being conducted by the Southwest Oncology Group (SWOG), 55 Stage I patients will be either observed or treated with gemcitabine plus cisplatin, based on ERCC1 and RRMI status.[18] RRM1 is a gene that has been shown to act as a predictor of gemcitabine efficacy.[19] The primary goal of the trial is an assessment of the feasibility of pharmacogenomics-based treatment assignment. The secondary outcome measures are two-year disease-free survival and analytical performance of the biomarker assay. Because patients will not be randomized to treatment, the disease prognosis vs. treatment prediction ability of ERCC1/RRMI cannot be differentiated. The relatively small sample size is also a limiting factor.

Investigators of an ongoing clinical trial being conducted by the Intergroup Francophone de Cancerologie Thoracique (IFCT) hypothesize that patients who receive therapy based on baseline tumor ERCC1 levels and EGFR mutations would attain better disease free survival rates than patients receiving noncustomized therapy. Patients with low ERCC1 levels will receive cisplatin plus pemetrexed (chemotherapy drugs) and those with high ERCC1 levels will not receive cisplatin-based chemotherapy. Those with EGFR mutations will be treated with erlotinib. This study will be conducted as both a phase II and phase III trial, where the standard chemotherapy arm will be in phase II and the customized treatment arm will be in phase III. The enrollment size is 108 patients with stage II/IIIA NSCLC.[20] This

trial also does not randomize the treatment and is relatively small. There are several other ongoing studies in this field but most focus on advanced stage NSCLC. This could be attributed to the small percentage of patients that are actually diagnosed with early stage NSCLC.

Figure 1: Ongoing clinical trials





Clinical Trial Implementation and Feasibility

No major issues expected other than low proportion of patients diagnosed with early stage NSCLC.

Market Factors

A review of medical/clinical policies at Regence, Anthem, BlueCross BlueShield of Tennessee, Cigna, and Aetna found no information related to ERCC1 expression testing. Medicare and its contractors have not issued a coverage decision on this test. The most likely explanation is that this test is not widely used and plans are not under pressure to make a determination of coverage at this point.

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Gene Expression Profile (GEP) in Multiple Myeloma

Test Purpose: Disease Prognosis and Identification of High-Risk Patients

<table>
<tr><th>Criteria</th><th>Profile</th></tr>
<tr><td>Indication – Population Impact</td><td>Estimated 20,580 annual cases and 10,580 deaths [1]. The 5-year survival rate is ~35%.</td></tr>
<tr><td>Current Standard of Care</td><td>Multiple combinations of the following treatments used: [1,2] Traditional Chemo: melphalan, doxorubin, cyclophosphamide. Corticosteroids: dexamethasone, prednisone. Immunomodulating Agents: thalidomide, lenalidomide. Proteasome inhibitor: bortezomib. Disease stage, physiological factors, and patient/oncologist preferences used to select therapy. Cytogenetic analysis often conducted, as patients with cytogenetic abnormalities (CAs) can benefit from certain specific treatments (such as bortezomib)</td></tr>
<tr><td>Strength of Association
(Clinical validity)</td><td>
<table>
<tr><th>Trial 2006-66: Treatment with bortezomib-lenalidomide-dexamethasone (VRD) N=177</th><th>Event-Free Survival</th><th>Overall Survival</th></tr>
<tr><td>High Risk (n=36, 23%) vs. non-high risk (n=123, 77%)</td><td>HR = 2.77; CI [1.18, 6.45]; p = 0.019</td><td>HR = 3.00; CI [1.23,7.31]; p = 0.016</td></tr>
</table>
</td></tr>
<tr><td>Potential Clinical Benefits
(Compared to current standard of care)</td><td>
<table>
<tr><th>Test Result</th><th>Potential Benefit</th><th>Population Impacted</th></tr>
<tr><td>High-Risk</td><td>Prediction of poor outcome
Early direction to clinical trials / aggressive chemotherapy</td><td>~20% of MM patients</td></tr>
<tr><td>Non High-Risk</td><td>Prediction of better outcomes
Therapeutic regimes with lower toxicities and AEs.</td><td>~80% of MM patients</td></tr>
</table>
</td></tr>
<tr><td>Potential Clinical Harms
(Compared to current standard of care)</td><td>
<table>
<tr><th>Test Result</th><th>Potential Harm</th><th>Population Impacted</th></tr>
<tr><td>High-Risk</td><td>Adverse events of experimental / aggressive chemotherapy</td><td>~20% of MM patients</td></tr>
<tr><td>Non High-Risk</td><td>None, since no change in treatment</td><td>~80% of MM patients</td></tr>
</table>
All cases:
Misclassification risk due to genetic testing errors, potential lack of standardization of expression methodology, and cut-offs
</td></tr>
<tr><td>Economic Impacts
Cost of therapies
Cost of test</td><td>Whole genome GEP test costs approximately $600[4].
Bortezomib – approximately $77,298 for 9 six-week cycles[5]</td></tr>
<tr><td>Evidence of Need
Likelihood evidence will change practice (value of information)</td><td>• Ongoing clinical trial in Denmark looks at the molecular characterization of multiple myeloma. Study enrollment – 200 newly diagnosed and relapsed patients[6]
• Ongoing phase II clinical trial evaluates the effect of lower and more frequent doses of chemotherapy on outcomes for 90 newly diagnosed or relapsed patients[7]
• No NCCN guidelines offered on use of GEP in MM</td></tr>
<tr><td>Clinical Trial Implementation and Feasibility</td><td>No major issues expected although given the relatively small prevalence of MM in the population, patient recruitment may be challenging.</td></tr>
<tr><td>Market Factors
Clearly defined and consistent coverage position</td><td>No Medicare national or local coverage decision for ERCC1 analysis testing. No information found at Regence, Anthem, BlueCross BlueShield of Tennessee, Cigna, Aetna, and Medicare.</td></tr>
</table>

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CANCERGEN Topic Brief

Genetic Expression Profile (GEP) in Multiple Myeloma (MM) to Identify Patients with Poor Prognosis

Test Purpose: Prognosis

Indication – Population Impact

Multiple myeloma (MM) is a disease of the plasma cells found in bone marrow. In the United States MM accounts for 1 percent of all cancers and 10 percent of hematologic cancers. In 2008-2009 there were approximately 20,580 cases and 10,580 multiple myeloma deaths. It is not curable and the survival rate is low (5-year post-diagnosis survival rate is approximately 35%)[1]. Slightly more men than women develop multiple myeloma and almost twice the number of blacks as compared to whites.
Multiple myeloma occurs most frequently in older adults; the average age at diagnosis is 65 years, with less than 2 percent under age 40. A 70-gene Gene Expression Profile (GEP) has been developed to assess the risk of disease progression in MM. Approximately 13% of patients are categorized as high-risk, and have lower 5-year survival (28% versus 78%, P<0.001; HR=5.16) than patients categorized as low risk [4].

Current Standard of Care

For the majority of patients with multiple myeloma, the goal of therapy is prolonging survival, relief of symptoms and disability due to the disease, and maximizing quality of life. Chemotherapeutic agents such as melphalan, doxorubin, and cyclophosphamide are used alongside immunomodulating agents such as thalidomide and its derivative lenalidomide to slow the progression of disease. More recently, bortezomib, a proteasome inhibitor, has been introduced to practice.

The combination of therapies employed depends upon disease stage, physiological factors, and patient/oncologist preferences. More aggressive regimens have more risk of toxicity but higher chances of response. Studies have shown that response rates are higher when Bortezomib is added to thalidomide and dexamethasone (VTD) (69%) when compared with thalidomide and dexamethasone alone (TD) (45%) [2].

Cytogenetic analysis (i.e. the large scale examination of chromosomes) is often conducted (and part of NCCN guidelines for initial diagnostic workup), as patients with cytogenetic abnormalities (CAs) can benefit from certain specific treatments (such as bortezomib). High-risk MM is routinely defined by laboratory parameters alone or in combinations in several staging systems. However, use of genetic analyses such as gene expression profiling (GEP) is currently not included in the NCCN treatment guidelines[3].

Strength of Genomic Association –Clinical Validity

The prognostic ability of the 70 GEP has been validated in MM; specifically, in multivariate analysis including the International Staging System and a gene-expression–based proliferation index, the 70-gene GEP remained a significant predictor of outcome. The 70-gene GEP has been shown to be effective in identifying high-risk patients undergoing monotherapy with bortezomib or high-dose dexamethasone[5].

Trial 2006-66 with 177 patients, employed bortezomib-lenalidomide-dexamethasone (VRD) maintenance for 3 years. The GEP identified 23% of patients as high-risk, and this subgroup (n=36)

exhibited significantly lowered event free survival (EFS) times (HR=2.77 CI [1.18, 6.45], p=0.019) and overall survival (OS) times (HR 3.00, 95% CI [1.23, 7.31], p=0.016). Over different trials, the GEP indication of high-risk patients retained independent prognostic significance.[6]

Trial 2006-66: Treatment with bortezomib-lenalidomide-dexamethasone (VRD) **N=177**	**Event-Free Survival**	**Overall Survival**
High Risk (n=36, 23%) vs. non-high risk (n=123, 77%)	HR = 2.77; CI [1.18, 6.45]; p = 0.019	HR = 3.00; CI [1.23,7.31]; p = 0.016

Potential Benefits

Patients classified as high-risk could either be directed to clinical trials for experimental treatments, and/or aggressive chemotherapeutic regimes – such as combination therapy with bortezomib, which may offer these patients improved survival outcomes. However their response to bortezomib in relation to low risk patients has not been clearly established.

Potential Harms

Patients assigned to the high-risk category may experience the side effects of experimental therapies and/or more aggressive chemotherapy regimes. Patients assigned to the non high-risk category do not experience any difference since the standard of care remains the same. However, in addition to the above, tests are imperfect and there is a risk that patients may be misclassified and receive unintended treatment.

Economic Impact

A gene expression profiling service offers the test of a whole genome for approximately $600 per sample[7]. The VISTA phase III trial[8] conducted by Millenium Pharmaceuticals used a dosing regimen for bortezomib of 1.3 mg/m^2 for 4 cycles with 8 injections in each cycle, followed by 5 cycles with 4 injections each. This approximates to a cost of $77,298 for 9 six-week cycles. The introduction of bortezomib as a management therapy is in addition to the cost of the standard treatment regimen. A GEP test may allow for expensive therapies to be administered to patients who would better respond to such treatments, although high-risk patients would most likely be enrolled in experimental studies.

Evidence of Need

There are several ongoing studies of GEP in MM. An observational study conducted by the Rigshospitalet in Denmark looks at the molecular characterization of multiple myeloma. The hypothesis is that early relapse depends both on the molecular defects in myeloma cells which are detectable with GEP as well as the acquisition of new mutations resulting in chemotherapy resistance. The primary outcome is to better understand the molecular characteristics by GEP within a 3 year time frame. The secondary outcomes relate to event free and overall survival. The estimated enrollment of 200 will include both newly diagnosed as well as relapsing patients [9].

A phase II clinical trial is being conducted at the University of Arkansas which with the goal of improving the remission rate and survival time for participants with high-risk myeloma. This is an interventional study with a single group assignment. Ninety newly diagnosed or relapsed MM patients will be

administered bortezomib on specific days of each treatment cycle. Investigators aim to find out if giving multi-agent chemotherapy in lower and more frequent doses will result in better treatment outcomes. The trial looks to perform gene expression profiling exams of CD-138 purified MM plasma cells and of bone marrow biopsy as a secondary outcome [10].

Clinical Trial Implementation and Feasibility

No major issues expected although given the relatively small prevalence of MM in the population, patient recruitment may be challenging.

Market Factors

A review of private payers shows no medical or coverage policies for the use of GEP in multiple myeloma. Examples of such payers are Regence, Anthem, Cigna and Aetna. No national or local coverage decisions have been issued by Medicare or its contractors.

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EGFR gene copy number (FISH) testing and cetuximab therapy in advanced non-small cell lung cancer (NSCLC)

<table>
<tr><th>Criteria</th><th>Profile</th></tr>
<tr><td>Indication – Population Impact</td><td>

196,454 annual lung cancer cases / 158,599 deaths[1]
80% lung cancers are NSCLC [2]
~35% of tumors are EGFR FISH positive [3]

</td></tr>
<tr><td>Current Standard of Care</td><td>

Platinum-based chemotherapy
Cetuximab + chemotherapy (per NCCN guidelines) but no FISH guidance
Cetuximab not FDA/EMA approved in lung cancer

</td></tr>
<tr><td>Strength of Association
(Clinical Validity)</td><td>
Median overall survival in SWOG S0342, concurrent arm (months)
<table>
<tr><td></td><td>[paclitaxel/carboplatin]</td><td>paclitaxel/carboplatin + cetuximab</td><td>Hazard Ratio</td></tr>
<tr><td>EGFR FISH positive</td><td>n/a</td><td>16 (n=25)</td><td>HR n/a</td></tr>
<tr><td>EGFR FISH negative</td><td>n/a</td><td>8 (n=15)</td><td>HR n/a</td></tr>
<tr><td>Hazard Ratio and p value or 95% CI</td><td></td><td>HR=0.43; P=0.03</td><td></td></tr>
</table>
Median overall survival in BMS-099 (months), N=104
<table>
<tr><td></td><td>taxane/carboplatin</td><td>taxane/carboplatin + cetuximab</td><td>Hazard Ratio</td></tr>
<tr><td>EGFR FISH positive</td><td>12.5 (n=27)</td><td>8.6 (n=27)</td><td>HR 1.92[1.05-3.54],, p=0.03</td></tr>
<tr><td>EGFR FISH negative</td><td>7.4 (n=24)</td><td>7.4 (n=26)</td><td>HR=0.84[0.47-1.52], P=0.57</td></tr>
<tr><td></td><td>HR=0.48; P=0.017</td><td>HR=1.07; P=0.81</td><td></td></tr>
</table>

Role of EGFR gene copy number determined by FISH in predicting cetuximab treatment response is unclear.

</td></tr>
<tr><td>Potential Clinical Benefits
(Compared to current standard of care)</td><td>
<table>
<tr><th>Standard Care</th><th>Potential Benefit</th><th>Population Impacted</th></tr>
<tr><td>Chemotherapy</td><td>Patients most likely to respond receive cetuximab</td><td>~35% of NSCLC patients (FISH+)</td></tr>
<tr><td>Chemotherapy + cetuximab</td><td>Patients less likely to respond avoid adverse events (AEs)</td><td>~65% of NSCLC patients (FISH-)</td></tr>
</table>
</td></tr>
<tr><td>Potential Clinical Harms
(Compared to current standard of care)</td><td>
<table>
<tr><th>Standard Care</th><th>Potential Harm</th><th>Population Impacted/ Grade 3+ AEs</th></tr>
<tr><td>Chemotherapy</td><td>Cetuximab AEs for FISH+ patients</td><td>~35% of NSCLC patients / 11% Rash, 5% Infusion reactions, 2% cardiac AEs</td></tr>
<tr><td>Chemotherapy + cetuximab</td><td>Patients less likely to respond receive cetuximab AEs.</td><td>~65% of NSCLC patients / 11% Rash, 5% infusion reactions, 2% cardiac AEs</td></tr>
</table>
All Cases: Misclassification due to genetic testing errors
</td></tr>
<tr><td>Economic Impacts</td><td>Cetuximab course of therapy ~$35,000 and EGFR FISH Test ~$800</td></tr>
</table>

Evidence of Need Likelihood evidence will change practice	The EGFR FISH test offers the potential to avoid high costs associated with cetuximab by determining whether patients will, in fact, benefit from this form of therapy.
Clinical Trial Implementation and Feasibility	• SWOG S0819 being conducted: " A Randomized, Phase III Study Comparing Carboplatin/Paclitaxel or Carboplatin/Paclitaxel/Bevacizumab with or without Concurrent Cetuximab in Patients with Advanced NSCLC." N=1546, Start = June '09; Est. Completion: June 2012 • Primary endpoint: OS for patients above, PFS of EGFR FISH+ patients • Secondary endpoint is OS and PFS of EGFR FISH+
Market Factors Clearly defined and consistent coverage position	EGFR FISH testing for NSCLC is considered investigational and not eligible for coverage. There is no private or Medicare policy coverage for the EGFR FISH assay.

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7. Assessment LBI-HT (September 2009) Horizon Scanning in Oncology Cetuximab (Erbitux®) in EGFR-expressing Non- Small Cell Lung Cancer

CANCERGEN Topic Brief

EGFR gene copy number (FISH) testing and cetuximab therapy in advanced non-small cell lung cancer (NSCLC)

Test Purpose: Disease Prognosis and/or Treatment Prediction

Indication – Population Impact

Lung Cancer is the most common cause of cancer death in the US; in 2006, 106,374 men and 90,080 women were diagnosed with lung cancer and 89,243 men and 69,356 women died from lung cancer[1]. Approximately 85% of lung cancer cases are classified as non-small cell lung cancer (NSCLC) and the majority of these patients are diagnosed with advanced disease for which there is no curative treatment.[2] The five-year overall survival (OS) of patients diagnosed with NSCLC is 15%.[2]

EGFR (epidermal growth factor receptor) exists on the cell surface and is activated by binding specific ligands, including the epidermal growth factor. Between 35-40% of patients have EGFR FISH-positive NSCLC tumors[3] Fluorescence in situ hybridization or FISH is an assay method.

Current Standard of Care

Platinum-based chemotherapy in combination with surgery and radiotherapy has been the established standard of care for advanced or metastatic NSCLC since the mid-1990s. First-line chemotherapy commonly uses a tandem treatment approach by incorporating cisplatin or carboplatin with agents such as paclitaxel, docetaxel, vinorelbine, gemcitabine, and, more recently, pemetrexed[3]. In 2009 the National Comprehensive Cancer Network (NCCN) added cetuximab as a first-line therapy for recurrent or metastatic NSCLC in patients with EGFR IHC-positive tumors. Immunohistochemistry or IHC refers to the process of localizing antigens or proteins in tissue samples by using labeled antibodies as specific reagents through antigen-antibody interactions that are visualized by a marker. It is important to keep in mind, however that IHC staining and the FISH assay are different tests (measuring protein expression and gene copy number respectively. A 2010 update to the NCCN guidelines, however, downgraded the combination of cetuximab/vinorelbine/cisplatin for 1st line therapy in metastatic and recurrent NSCLC, from a Category 2A to a Category 2B recommendation [4].

Even though cetuximab is recommended for lung cancer treatment by the NCCN guidelines (with no specifics regarding EGFR FISH testing), it is not currently FDA approved for any lung cancer indication. Some evidence exists suggesting that it may result in a modest (~1 month) survival benefit in lung cancer. In the FLEX trial[6], 1125 chemo-naïve NSCLC patients (Stage IIIB+) expressing EGFR IHC+ tumors were randomized to chemotherapy + cetuximab (n=557), or chemotherapy alone (n=568). Median overall survival for the cetuximab + chemotherapy was 11.3 months vs. 10.1 months (HR=0.871 [0.762-0.996, p=0.044]). Major adverse effect (AE) (Grade3+) was rash (10%).

FLEX Trial[6], Phase III, 1125 chemo-naïve NSCLC patients (Stage IIIB+) expressing EGFR IHC+ tumors		
Median Overall Survival		
Chemotherapy (n=568)	Cetuximab + Chemotherapy (n=557)	Hazard Ratio and p value or 95% CI
10.1 months	11.3 months	HR=0.871 [0.762-0.996], p=0.044

Strength of Association – Clinical Validity

Gene copy number (FISH) and protein over-expression (IHC) are somewhat correlated (r=0.4).[5] These tests are also different from EGFR mutation testing (which is relevant for erlotinib therapy). There are currently no NCCN guidelines addressing the use of the EGFR FISH assay for cetuximab use in NCSLC. However, EGFR mutation testing is recommended in the pathology section (molecular diagnostics) of the guidelines for the initial patient workup (to guide erlotinib use in some EGFR mutation+ patients).

In the SWOG S0342 Phase II trial [7], 229 chemo-naïve patients with advanced stage lung cancer (Stage IIIB+) were randomized to either concurrent or sequential chemotherapy (paclitaxel + carboplatin) + cetuximab. Because patients were not randomized to +/- cetuximab, the prognostic vs. predictive ability of EGFR FISH testing for cetuximab cannot be discerned from these results. However, based on the clinically significant differences in OS, it appears that FISH testing has relevant prognostic or predictive properties (or both) for these treatment regimens.

Median overall survival in SWOG S0342, concurrent arm (months)

	[paclitaxel/carboplatin]	paclitaxel/carboplatin + cetuximab	Hazard Ratio
EGFR FISH positive	n/a	16 (n=25)	HR n/a
	n/a	8 (n=15)	HR n/a
Hazard Ratio and p value or 95% CI		HR=0.43; P=0.03	

In the BMS-099 trial, 676 chemo-naïve patients with Stage IIIB+ NSCLC who were free of any histology or EGFR expression status were assigned to taxane/carboplatin, or taxane/carboplatin + cetuximab. The difference in OS based on EGFR FISH status in cetuximab patients was not as dramatic as in the S0342 study. Furthermore, EGFR FISH positive patients treated with cetuximab had significantly lower OS than those treated with chemotherapy alone.

Median overall survival in BMS-099 (months), N=104

	taxane/carboplatin	taxane/carboplatin + cetuximab	
EGFR FISH positive	12.5 (n=27)	8.6 (n=27)	HR 1.92 [1.05-3.54], p=0.03
EGFR FISH negative	7.4 (n=24)	7.4 (n=26)	HR=0.84 [0.47-1.52], P=0.57
HR and p value or 95% CI	HR=0.48; *P*=0.017	HR=1.07; *P*=0.81	

In summary, the role of EGFR gene copy number in predicting response to cetuximab treatment in NSCLC is unclear based on studies to date.[9]

Potential Benefits

The potential benefits of adding cetuximab to chemotherapy for FISH (+) patients is difficult to assess given the conflicting studies discussed above. If platinum-based adjuvant therapy is the standard of care, FISH (-) patients who are prescribed platinum-based therapy alone will avoid the adverse effects of cetuximab, and FISH (+) patients may receive the benefit of cetuximab treatment if such a benefit (vs. harm) can be confirmed.

Potential Harms
The potential harms of adding cetuximab to chemotherapy for FISH (+) patients are difficult to assess given the conflicting studies discussed above. If platinum-based adjuvant therapy is the standard of care, FISH (-) patients who are prescribed platinum-based therapy alone would not receive any potential benefit from cetuximab treatment.

However, in addition to the above, tests are imperfect and there is a risk that patients may be misclassified and receive unintended treatment.

Economic Impact
Cetuximab is priced at $1,421 for each vial 100 ml vial with 5mg/ml of solution. An initial starting dose of 400 mg/m^2 is administered, leading to a cost of $2,874. This is followed by a maintenance dose of 250 mg/m^2 each week yielding a cost of $1,796/week. The median duration of treatment of 18 weeks, as presented in the FLEX trial, was used to calculate a maintenance cost of $32,336. The total cost for using cetuximab is thus approximately $35,210.[10] These costs are in addition to a platinum-based double-agent chemotherapy regime. The cost of the EGFR FISH assay is estimated to be around $794.

Evidence of Need
There are relatively few studies looking at predictive capabilities of the test. As illustrated above, costs associated with using cetuximab are significant and the ability to tailor treatment could be valuable. Based on the BMS study described above, EGFR testing does not offer any benefit in FISH-negative patients.

One ongoing observational study is investigating laboratory samples from 30 NSCLC patients to identify mutations in EGFR using different types of tests, one of which is FISH. This is a multicenter study where the primary outcomes are to identify EGFR mutations and investigate EGFR DNA copy-number changes[10].

A phase II ongoing clinical trial conducted by Bristol-Myers Squibb is investigating whether EGFR status by FISH can predict response to cetuximab therapy in NSCLC patients treated with carboplatin and paclitaxel. The trial was designed to look at progression free survival as a primary outcome with 260 patients. This study was withdrawn, possibly due to enrollment issues.[11].

The Southwest Oncology Group is currently conducting a phase III study comparing overall survival in patients with stage IV or recurrent NSCLC treated with carboplatin, paclitaxel and bevacizumab with versus without cetuximab. Overall and progression-free survival amongst FISH-positive patients will also be investigated. Planned study enrollment is 1546 patients[14]

Clinical Trial Implementation and Feasibility
SWOG is currently conducting a phase III study in this area.

Market Factors
The medical policies of private health plans reviewed found no coverage decisions addressing the use of EGFR FISH assay for cetuximab use in NSCLC. Examples of these policies include Anthem, Regence, and BlueCross BlueShield of Tennessee. Medicare and its contractors have also not issued a national or local coverage decisions. Since this test is not widely used and there is not an NCCN guideline addressing FISH, it is likely that public and private payers have not seen the need to formulate a medical policy or coverage decision on the test

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Carcinoembryonic Antigen (CEA) and Cancer Antigen (CA) 15-3 and CA 27.29 markers for detection of recurrence after primary breast cancer therapy

Criteria	Profile
Indication – Population Impact	• 191,410 new cases of breast cancer annually • Five-year recurrence rates are 7%, 11%, and 13% for women with stages I, II, and III disease, respectively. [1] • CA15-3 levels elevated in <10% of early-stage and ~70% of advanced stage breast cancer [2]. • CA 27-29 levels elevated in 33% of early-stage and 67% of late-stage breast cancer [3]. • CEA levels elevated in 19% of smokers and 3% of healthy controls.[3]
Current Standard of Care	2006/2007 ASCO recommendations do not support the use of CA 15-3 and CA 27.29 tumor markers alone for monitoring patients for recurrence after primary breast cancer therapy.
Strength of Association (Clinical validity)	**CA 15-3 tumor marker** • Patient sensitivity of CA 15-3 is reportedly 36%, specificity as high as 97%. • Positive predictive value - 78% and negative predictive value – 82% • With elevated tumour marker, recurrent disease could be confirmed in approximately 4 out of 5 patients[4] **CA 27-29 tumor marker** • Sensitivity of CA 27-29 57%, specificity 98% in detecting recurrence[5]. • CA 27-29 testing identifies recurrence an average of 5.3 months before other symptoms or tests, but testing does not improve survival rates.[5] **CEA tumor marker** • No relevant studies identified by 2007 ASCO guidelines.
Potential Clinical Benefits	In theory, earlier detection of recurrence might afford earlier treatment that in turn could improve quality of life and/or survival
Potential Clinical Harms	False positive results will lead to high numbers of unnecessary evaluations that could cause morbidity (e.g., additional biopsies) and patient anxiety
Economic Impacts Cost of therapies Cost of test	• Cost of CEA, CA 15-3, CA 27-29 is ~ $500.[6]
Evidence of Need Likelihood evidence will change practice	• Recommendations against the use of tumor serum markers are based on outdated studies (from the 1980s)[7]. • Roger Williams Medical Center – conducting a study with 26 samples on modification of T cells to offer better response to tumor markers[8] • Physician usage is being determined.
Clinical Trial Implementation and Feasibility	SWOG is developing a study concept “A Phase II Clinical Trial Evaluating the Financial and Psychological Impacts of Serial Laboratory and Imaging Testing in Routine Follow-up of High-Risk, Stage II-III Breast Cancer Survivors”
Market Factors Clearly defined and consistent coverage position	Medicare covers CEA, CA 15-3 and CA 27-29 for women with breast cancer [9]

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CANCERGEN Topic Brief

Carcinoembryonic Antigen (CEA) and Cancer Antigen (CA) 15-3 and CA 27-29 markers for detection of recurrence after primary breast cancer therapy

Test Purpose: Prognostic for Recurrence of Breast Cancer

Indication – Population Impact

Breast cancer is the most common cancer among women in the United States with the exception of skin cancers. There are approximately 2.6 million women living in the U.S. with a history of breast cancer. Approximately 190,000 new cases of invasive breast cancer are diagnosed each year and an estimated 40,000 women will die from breast cancer each year[1]. Five-year survival for women diagnosed with localized breast cancer (confined to primary site) is 98%. Five-year relative survival for regional breast cancer (spread to regional lymph nodes) is 84%.[2] Comparatively, 5-year recurrence rates are 7%, 11% and 13% for women with stages I, II and III disease, respectively.[3]

The tumor markers CA15-3, CA27-29 and CEA are three serum antigens used for predicting breast cancer recurrence, and detection of these markers may alert healthcare providers to the recurrence of breast cancer during surveillance, when conventional techniques (such as physical exams and mammograms) are not able to. Elevated levels of the tumor marker CA15-3 is detected in <10% of early-stage and ~70% of advanced stage breast cancer.[4] The marker CA27-29 is elevated in 33% of early-stage and 67% of late-stage breast cancer.[5] In general, levels of the marker CEA are elevated in 19% of smokers and 3% of healthy controls.[5]

Current Standard of Care

ASCO 2006 breast cancer follow-up guidelines recommends physical examinations, breast self examinations, and mammography for women undergoing treatment for breast cancer with curative intent at local or regional stages.[6] Specifically, examinations should be performed every 3 to 6 months for the first 3 years, every 6 to 12 months for years 4 and 5, and annually thereafter. The guidelines further state that, "the use of … tumor markers (carcinoembryonic antigen, CA 15-3, and CA 27.29) is not recommended for routine breast cancer follow-up in an otherwise asymptomatic patient with no specific findings on clinical examination."[6]

Analogously, ASCO 2007 tumor marker guidelines state that, "Present data do not support the use of CA 15-3 and CA 27.29 alone for monitoring asymptomatic patients for recurrence after primary breast cancer therapy." However, the guidelines state that during active therapy CA 15-3 and CA 27-29 can be used in conjunction with diagnostic imaging and history and physical examination to evaluate treatment response.[7] In the absence of measurable disease, an increase in tumor marker levels may be interpreted to indicate treatment failure.

Strength of Genomic Association – Clinical Validity

A study was conducted in Finland in 2001 where 243 breast cancer patients, diagnosed between 1991 and 1995, were followed prospectively after primary treatment until first relapse. Both sensitivity and specificity were analyzed in different metastatic situations over the 5 years. Patient sensitivity, defined

as the number of relapsed patients with positive tumour markers among all of the relapsed patients, was 36%, while specificity, estimated as the number of patients with Ca 15-3 in the normal range among those without relapses, was 97%. However, 3% of patients without recurrence will have elevated CA 15-3 levels (false positive results). Moreover, monitoring with the use of CA 15-3 levels has shown no demonstrated impact on survival[8].

CA 27-29 has been reported to have a sensitivity of 57%, a specificity of 98%, a positive predictive value of 83%, and a negative predictive value of 93% in detecting breast cancer recurrences. CA 27-29 has been found to identify recurrence an average of 5.3 months before symptoms appear. However, the study was not designed to evaluate a survival outcome, and there was thus not a demonstrated impact on outcomes such as overall survival and disease free survival.[9]

The ASCO 2007 Guidelines did not identify any relevant studies for the CEA marker.

Potential Benefits

Earlier detection of recurrence might afford earlier treatment that in turn could improve quality of life and/or survival.

Potential Harms

Poorly predictive tests could lead to high numbers of unnecessary evaluations that could cause morbidity (e.g., additional biopsies) and patient anxiety.

Economic Impact

The Breast Cancer Monitoring Panel test offered by Any Lab Test in Houston, TX is priced at approximately $500 and includes testing for CEA, CA 15-3 and CA 27-29[10]. Note that Medicare's payment for these tests is ~ $30 each. Evaluation of 'positive' test results would lead to moderate increases in healthcare cost.

Evidence of Need

There are few studies being conducted with regards to using breast cancer markers for detection of recurrence. Massachusetts General Hospital is investigating the effects of using aromatase inhibitor therapy on breast cancer patients. The primary goal is to measure the proportion of patients that have a decline in CA 15-3 once letrozole (an aromatase inhibitor) therapy has been reintroduced after a drug free observation phase. Both CA 15-3 and CA 27-29 will be measured each week to guide decision making on when to re-start letrozole therapy. The study will only be conducted on 18 postmenopausal women with metastatic breast cancer[11].

Roger Williams Medical Center is conducting a study that investigates the safety and effectiveness of second-generation T cells in patients with breast cancer. T cells will be extracted from the patient and modified in a laboratory so that they recognize and target the tumor antigen, CEA. Note that only 26 samples will be used for this trial. Most ongoing trials focus on modification of T cells and how they can respond better to CEA, CA 15-3 and CA 27-29 [12].

The recommendation against the serial use of serum tumor markers to detect recurrence after primary breast cancer therapy is based on an absence of data showing benefit in terms of clinical outcomes, including improvements in overall or disease-free survival, improvement in quality of life and/or global

health outcomes, reduced toxicity, or improved cost effectiveness. Two prospective, randomized trials performed in Italy in the mid 1980s compared standard versus intensive follow-up regimens in women with early stage breast cancer[13]. Neither study showed a difference in overall survival between the two arms at 5 years.

The findings of these studies are frequently cited as proof that early detection of breast cancer recurrence and early initiation of therapy is of no benefit to the patient. These studies were performed in the mid-to-late 1980s, an era with vastly different treatment options for those diagnosed with relapse. A compelling reason to study methods to improve the early detection of breast cancer recurrence at this time is the availability of a multitude of newer therapies for breast cancer, with favorable efficacy and toxicity profiles. In the past, the primary therapeutic option for metastatic breast cancer recurrence was chemotherapy. New hormonal agents (third generation aromatase inhibitors, selective estrogen receptor modulators), biological agents (trastuzumab, lapatinib, bevacizumab) and chemotherapeutic agents (taxanes, capecitabine, gemcitabine, epothilones) are all examples of metastatic breast cancer therapies introduced within the past decade, several of which have dramatically impacted survival when used in the adjuvant setting.

Clinical Trial Implementation and Feasibility

SWOG is developing a study concept "A Phase II Clinical Trial Evaluating the Financial and Psychological Impacts of Serial Laboratory and Imaging Testing in Routine Follow-up of High-Risk, Stage II-III Breast Cancer Survivors"

Market Factors

Several private payers and Medicare cover CA 15.3 and CA 27.29 in the follow up and management of advanced breast cancer. Specifically, Cigna considers CA 15.3 and CA 27.29 medically necessary to monitor the treatment of patients with advanced breast cancer and for the follow-up of breast cancer in a symptomatic patient. Aetna considers CA 15-3 and CA 27-29 medically necessary in following the course of treatment in women diagnosed with breast cancer, especially advanced metastatic breast cancer, and states that an increasing CA 15-3 level may suggest treatment failure. BlueCross BlueShield of Tennessee considers CA 15-3 and CA 2-29 medically necessary as adjuncts in the follow-up and management of metastatic breast cancer when elevated levels of these markers would change the treatment option. The use of these tumor markers as a screening tool when symptoms are not present is considered investigational. Medicare (CMS) has issued a National Coverage Decision (NCD) stating that multiple tumor markers "are available for monitoring the response of certain malignancies to therapy and assessing whether a residual tumor exists post-surgical therapy. CA 15-3 is often medically necessary to aid in the management of patients with breast cancer. Serial testing must be used in conjunction with other clinical methods for monitoring breast cancer. For monitoring, if medically necessary, use consistently either CA 15-3 or CA 27.29, not both. CA 27.29 is equivalent to CA 15-3 in its usage in management of patients with breast cancer."

BlueCross BlueShield of Tennessee considers CEA investigational for the diagnosis, monitoring, or prognosis determination of breast cancer. Aetna considers CEA investigational for screening, diagnosis, staging or routine surveillance of breast cancer. Cigna considers CEA investigational for the screening,

diagnosis, staging, or routine follow-up for patients with lung or breast cancer after primary therapy. CMS has an NCD on CEA stating that it may be medically necessary for patients with metastatic solid tumors which express CEA. It may be measured at the start of the treatment and with subsequent treatment cycles to assess the tumor's response to therapy. Medicare would cover CEA for metastatic breast cancer, but not primary breast cancer, to monitor the course of treatment.

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