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Dear Dr. Quinn:

I am writing concerning the draft statements relating to "Oncologic in vitro chemoresponse assays [hereafter abbreviated as IVCA]-Noncoverage" appearing on your website (as accessed April 12, 2006). I only just now learned of this review and of the fact that this topic is to be on the agenda of your April 17 and April 19 meetings.

I have a number of specific comments relating to IVCA technology and data, but I'd like to begin with the following quotation from your brief draft review:

*"In 2004, reports were published by the American Society of Clinical Oncology (ASCO) and the Blue Cross "TEC" technology evaluation committee. The ASCO report concluded flatly that,*

*"The use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient's health status and treatment preferences.' "*

Your draft review goes on to note three additional points, relating to (1) uniform criteria for LCD and NCD determinations, (2) positions of national associations and/or the Blue Cross TEC committee, and (3) consensus medical statements and association statements. The review concludes that "in vitro chemosensitivity tests" are not covered per Medicare's NCD (quoting 190.17; n.b. I believe that the correct reference should be 190.7, Rev. 1, 10-03-2003). You are apparently now deciding to add "the reciprocal tests" (i.e. so-called chemoresistance tests) as a non-covered LCD.

I believe that your draft decisions are based on the most superficial of evaluations and will not withstand future scrutiny and challenges. Furthermore, these decisions are a disservice to Medicare beneficiaries. Finally, these decisions are cost-ineffective.

We must begin by realizing that drug selection in cancer is a grave and daunting challenge. In the absence of information provided by IVCA, on what basis are drugs selected?

ASCO states that "oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient's health status and treatment preferences."

In theory, this is all well and good, but how does this advice work in the real world of cancer chemotherapy?

I could take this disease by disease and make precisely the same points that I shall make below in almost all situations, but, for purposes of simplification, I shall consider breast cancer as a prototype for the rest of my remarks. This choice is appropriate, for more chemotherapy is given for breast cancer than for any other form of cancer and there have been more "published reports of clinical trials" for breast cancer than for any other form of cancer. Also, there are well established (and emerging new, e.g. the "OncotypeDX") tests which are widely used in breast cancer to assist in treatment selection; so there are useful precedents with respect to comparing and contrasting IVCA.

ASCO says that treatment decisions should be based on "published reports of clinical trials" and "a patient's health status," and patient "treatment preferences."

How about "published reports of clinical trials?"

Here is the "state of the art chemotherapy" in recurrent or metastatic breast cancer, according to the NCI's official cancer information website (quotations and drug listings below excerpted March 31, 2006)

***"Whether single-agent chemotherapy or combination chemotherapy is preferable for first-line treatment is unclear."***

***"At this time, no data support the superiority of any particular regimen."***

And what are the regimens which the NCI deems as being equally efficacious, on the basis of "published reports of clinical trials?"

The NCI statement summarizes these as following (verbatim quotation follows):

"Single agents that have shown activity in metastatic breast cancer:

Anthracyclines.

Doxorubicin, Epirubicin, Liposomal doxorubicin, Mitoxantrone.

Taxanes.

Paclitaxel, Docetaxel, Albumin-bound nanoparticle paclitaxel (ABI-007 or Abraxane)

Alkylating agents.

Cyclophosphamide.

Fluoropyrimidines.

Capecitabine,5-FU.

Antimetabolites.

Methotrexate.

Vinca alkaloids.

Vinorelbine.Vinblastine.Vincristine. [continued on next page]

Platinum.  
Carboplatin,Cisplatin.  
Other.  
Gemcitabine.Mitomycin C.

"Combination regimens that have shown activity in metastatic breast cancer

CA: cyclophosphamide and doxorubicin.  
Docetaxel and doxorubicin.  
CAF: cyclophosphamide, doxorubicin, 5-fluorouracil.  
CMF: cyclophosphamide, methotrexate, 5-fluorouracil.  
Doxorubicin and paclitaxel.  
Docetaxel and capecitabine.  
Vinorelbine and epirubicin."

It would appear that "published reports of clinical trials" provide precious little in the way of guidance. It should be also noted that three decades of such "published reports of clinical trials" in trials performed on literally hundreds of thousands of patients have not resulted in the slightest hint of improved survival for these patients, the median of which remains below 2 years. But all the above treatments are clearly not equal on an individual basis, as there are innumerable patients who have progressive disease on first line therapy, only to enjoy a dramatic benefit from second or even third line therapy, and these patients would have been much better served by receiving the most probably active treatment the first time around.

In the total absence of guidance from "published reports of clinical trials," on what basis are treatment regimens selected in the real world?

ASCO says that this should be further based on: "a patient's health status" and patient "treatment preferences."

Is this what is being done?

On December 8, 1999, I called attention to the fact that medical oncologists in private practice were deriving most of their income by running a retail pharmacy concession, in testimony I gave to the National Medicare Executive Committee in Baltimore (verbatim transcript of my remarks at the time available upon request).

Just published in the journal Health Affairs is a joint Harvard/Michigan study entitled "Does reimbursement influence chemotherapy treatment for cancer patients?" In a study of 9,357 patients, the authors documented a clear association between reimbursement to the oncologists for the chemotherapy of breast, lung, and colorectal cancer and the regimens which the oncologists selected for the patients. In other words, oncologists tended to base their treatment decisions on which regimen provided the greatest financial remuneration to the oncologist (Jacobson, M.,O'Malley, A.J., Earle, C.C., et al. Health Affairs 25(2):437-443, 2006).

The following is a link to the March 8, 2006 New York Times article describing the study:

<http://www.nytimes.com/2006/03/08/health/08docs.html>

One of the more interesting aspects of this story is the following:

[Quoted from the above New York Times article]:

"An executive with the American Society of Clinical Oncology, Dr. Joseph S. Bailes, disputed the study's findings, saying that cancer doctors select treatments only on the basis of clinical evidence. 'All of us are looking at clinical trials,' he said."

So ASCO's Dr. Bailes maintains that drugs are chosen only on the basis of "clinical evidence." Well, here is what is peculiar:

Neil Love, MD reported a survey of (1) breast cancer oncologists based in academic medical centers and (2) community based, private practice medical oncologists. The former oncologists do not derive personal profit from the administration of infusion (i.v.) chemotherapy, the latter oncologists do derive personal profit from infusion (i.v.) chemotherapy, while deriving no profit from prescribing oral-dosed chemotherapy. The results of the survey could not have been more clear-cut. For first line chemotherapy of metastatic breast cancer, 84-88% of the academic center-based oncologists (who are motivated to keep off-protocol patients out of their chemotherapy infusion rooms to reserve these rooms for on-protocol patients) prescribed an oral dose drug (capecitabine), while only 13% prescribed infusion (i.v.) drugs, and none of them prescribed the expensive, highly remunerative drug docetaxel. In contrast, among the community-based oncologists, only 18% prescribed the non-remunerative oral dose drug (capecitabine), while 75% prescribed remunerative infusion (i.v.) drugs, and about 40% prescribed the expensive, highly remunerative drug docetaxel

<http://patternsofcare.com> see figure 37, volume 2, issue 1, 2005

The existence of this profit motive in drug selection has been one of the major factors working against the individualization of cancer chemotherapy based on testing the cancer biology.

Recently, Public Interest Watch has called for a government investigation into ASCO, for the manipulative ways in which it has attempted to scuttle badly-needed reforms in this inherently corrupt system.

The press release below cites a recent Associated Press account of maneuverings by ASCO in its attempts to preserve its lucrative "chemo concession."

<http://www.susanlovemd.org/community/flashes/in-the-news/news030126.htm>

[http://www.publicinterestwatch.org/press\\_9\\_8\\_04.htm](http://www.publicinterestwatch.org/press_9_8_04.htm)

"...we believe the American Society of Clinical Oncologists is just as at fault as Ketchum. ASCO's decision to retain Ketchum appears to be nothing more than a premeditated attempt to corrupt the legislative process and to waste millions in public funds in the process."

"ASCO has run into trouble before in the course of its campaign against Medicare reform. In March, the editorial board of the New York Times criticized "angry doctors" for "terrorizing their patients" into believing that a reformed Medicare drug reimbursement plan would force them to turn cancer patients out to less convenient and less comfortable hospitals for chemotherapy treatment. ("Cancer Scare Tactics," March 22, 2004, New York Times)"

Now is as good a time as any to consider the issue of cost to the health care system relating to coverage for IVCA.

The cost of IVCA is truly a drop in the bucket compared to the costs associated with infusion chemotherapy. In the absence of IVCA, oncologists will continue to base their drug selections on reimbursement more than on any other single factor. Those oncologists who order IVCA do so at their own personal financial disadvantage. Absent the testing, they are free to choose what for them is the most remunerative therapy. When they order the tests, they do so either because they themselves want to choose the treatment which is most likely to work or else, increasingly, that this is what their patients want (and remember that even ASCO endorsed the patient's "treatment preferences"). Either way, they are forced to consider information going beyond reimbursement. The worst case scenario, cost-wise, is that the treatment chosen with the benefit of the IVCA information will be the same, expensive treatment that they'd otherwise choose on the basis of reimbursement. In a better case scenario, treatment based on IVCA will be more efficacious therapeutically; although it may not be the most remunerative to the oncologist, it will benefit the patient, be less expensive, and save money for the health care system.

I'd like to move now to a consideration of the various TEC reviews, which you (NHIC) are now considering and, of equal importance, those which you have failed to consider.

It seems obvious that you are basing your current actions mainly on the two reviews published in the September, 2004 issue of the Journal of Clinical Oncology, and coverage recommendations directly arising from these two reviews (by the Blue Cross National TEC committee and by ASCO). These reviews (and resulting recommendations) are fatally flawed for a number of reasons. There are better independent reviews which you failed to consider.

Don't be fooled, also, by the comparatively recent date of these two September, 2004 reviews. They are simply a recycling of old data and arguments previously published in

the mid to late 1990s and are much less current and certainly much less relevant than more thoughtful reviews with earlier publication dates (to be discussed below).

The Blue Cross TEC and ASCO reviews are fatally flawed for the following reasons:

1. Both reviews failed to use the well established criteria (used by the FDA and all other relevant agencies) for evaluating laboratory tests that are used as a guide for treatment selection. Both BC TEC and ASCO reviews invented a novel and unprecedented criterion never before applied to any analogous laboratory test (e.g. estrogen receptor, progesterone receptor, Her2/neu, immunohistochemical pathology for classification of tumors for treatment selection) and which is a criterion not being applied to any other analogous laboratory tests currently being proposed and developed for clinical application (e.g. the "OncotypeDX" test, EGFR gene mutation and amplification tests, etc.). The BC TEC/ASCO criterion has also not been applied to expensive radiographic (e.g. PET/CT) tests performed to monitor tumor response to treatment solely for the purpose of determining if a given treatment should be continued or changed. More on this below.

2. Both reviews were completely closed, in that neither BC TEC nor ASCO sought nor allowed input or pre-decision review from outside experts in the field of the performance and utilization of IVCA. This is in contradistinction to the superior reviews by California Blue Shield's nationally respected TEC and by a national Medicare review (both discussed below), which actively sought and considered pre-meeting data submissions and written commentaries, then invited oral presentations, then allowed for open debate between both proponents and opponents, and then had open, transparent discussions and (in the case of California BS TEC) open balloting. California Blue Cross, in contrast, used to provide coverage for IVCA when it was a non-profit, but later revoked this coverage when it became a for-profit, and has never had open TEC meetings nor allowed for any sort of meaningful debate in their completely opaque coverage considerations.

With respect to point number 1 (above):

The traditional (and only) criteria ever used to evaluate laboratory (or similar predictive/prognostic) tests has been the predictive accuracy (sensitivity/specificity) of the test in question. Yet both BC TEC and ASCO reviews specifically EXCLUDED from consideration all studies reporting the predictive accuracy of the tests! In the words of the ASCO review authors: "We excluded reports that only reported correlations between assay results and clinical outcomes" (where "outcomes" are both response to treatment and patient survival). Instead, the ASCO authors included for consideration only on old, previously-reviewed studies comparing outcomes of patients who had treatment based on assay results versus patients with empirically chosen therapy. Likewise, the BC TEC authors specifically excluded studies pertaining to the predictive accuracy of IVCA and only included studies relating to comparisons of treatment outcomes for assay-guided versus empiric therapy.

On superficial consideration, the criteria of laboratory assay "efficacy" (as opposed to laboratory assay "accuracy") sounds reasonable, but it is both unprecedented and unfair.

To begin with, none of the available laboratory tests used in the selection of treatments for cancer patients have ever been tested for "efficacy," and this includes estrogen receptor, progesterone receptor, Her2/neu, immunohistochemical staining for tumor classification, bacterial culture and sensitivity testing, CT, MRI, and/or PET scans to measure tumor "response" to treatment -- as opposed to basing assessment of clinical response on simple/cheap history, physical, routine labs, routine radiographs, etc. All of these tests are used to guide treatment and drug selection no less than are IVCA, yet the only data supporting any of them relate to test accuracy and there is a total lack of information regarding test efficacy. Likewise, no one is seriously proposing that any of the "molecular" tests now available (e.g. OncotypeDX, EGFR amplification/mutation) should have to be proven "efficacious" (as opposed to "merely" accurate) before they are used in clinical decisions regarding treatment selection.

Additionally, the BC TEC and ASCO reviews may imply that there have been good studies done to examine the issue of "efficacy," when the true situation is that the IVCA technologies are all public domain, non-proprietary and no private sector companies or individuals should reasonably be expected to pay for such unprecedented studies and none of the granting agencies has ever been willing to support such studies, also. So it is hereby stipulated that there is no literature establishing clinical "efficacy" of IVCA, because the costs of such clinical trials are prohibitive, support is non-existent, and no other analogous tests have been or will likely ever be subjected to such an unreasonably high bar criterion for clinical use, as well.

It should be noted that, while the FDA doesn't regulate clinical laboratories performing "home brew" tests, it does regulate test kits. In the 1990s, the FDA formally approved a Baxter test kit for IVCA testing, based entirely upon demonstration of acceptable test accuracy in a single, small published study, and did not require proof of "efficacy," as, again, this remains an unprecedented criterion for evaluating any laboratory test.

In point of fact, IVCA has been well proven to have predictive accuracy which compares very favorably with that of comparable tests, such as estrogen receptor, progesterone receptor, Her2/neu and the newer "molecular" tests. IVCA predicts for response and patient survival in a wide spectrum of neoplasms and with a wide spectrum of drugs. I would be very happy to provide a comprehensive, up to date review of all of these data, given a reasonable time to update my prior reviews (the most recent of which was in 2002, but many additional studies have been carried out since then).

In light of the true situation, in which there is precious little in the way of guidance from clinical trials with respect to "best" empiric therapy (e.g. see above example of recurrent/metastatic breast cancer), where the only thing which has been proven to correlate with treatment decisions is reimbursement to the prescribing oncologist, and where even ASCO recognizes the importance of basing cancer treatment at least in part on patient preferences, it is entirely unreasonable not to support the judicious application

of laboratory tests which have been well characterized with respect to test accuracy, if not (for entirely understandable reasons) for test "efficacy."

I'd like to move now to address errors and omissions relating to the following in your draft coverage policy, relating to (1) uniform criteria for LCD and NCD determinations, (2) positions of national associations and/or the Blue Cross TEC committee, (3) consensus medical statements and association statements, and (4) your final comment that that "in vitro chemosensitivity tests" are not covered per Medicare's NCD (quoting 190.17; n.b. I believe that the correct reference should be 190.7, Rev. 1, 10-03-2003).

To address point number (4) first:

This statement is very misleading. The National Coverage Decisions described in 190.7 ("Human Tumor Stem Cell Drug Sensitivity Assays") clearly and explicitly apply to two and only two specific (and long abandoned) technologies, namely the "human tumor stem cell" (also known as "cloning" or "clonogenic") assay and the "Fluorescent Cytoprint Assay" (the latter a test previously offered by a long (i.e. 20 year) defunct Rhode Island laboratory called Analytical Biosystems). Neither of these technologies are even, to my knowledge, available anywhere today as a clinical service for patients. As discussed below, Medicare specifically declined to formulate a National Coverage policy relating to the technologies which are available and being used today, most specifically (in the context of my present letter) including assays based on measuring apoptotic death of cells in short term suspension cultures (e.g. DISC and MTT endpoints), for which a large and compelling body of data exist to establish clinical relevance.

I'd like to discuss the two fairest and best and most recent (notwithstanding publication dates) reviews of the clinical appropriateness of IVCA, these being the national Medicare TEC review in November of 1999 and the two California Blue Shield TEC reviews in the mid to late 1990s.

Considering first the Blue Shield TEC reviews:

On March 2, 1994, I attended the meeting of the Blue Shield of California Medical Policy Committee on Quality and Technology, held in San Francisco. There were 5 topics on the March 2 agenda. Two of these were of importance to oncology. The first topic was autologous bone marrow transplantation therapy of breast cancer. Proponents from major California transplant programs presented data favoring a policy of reimbursement. Much of the debate had to do with the strength of the uncontrolled trials, patient selection bias, and related issues. However, Dr. Craig Henderson (Director of Clinical Oncology at UCSF) argued persuasively against reimbursement, pending availability of data from ongoing randomized trials, and the vote was unanimous (20 to 0) against reimbursement. A subcommittee was to be formed to monitor the flow of new data from the ongoing trials.

The next oncology topic was the reconsideration of cell culture assays to identify "bad" and "good" cancer chemotherapy drugs, prior to patient treatment. This topic had been previously considered at the October 13, 1993 meeting, but was tabled for 5 months after vigorous debate. The debate on March 2, 1994, was interesting, as the Northern California Oncology Association opposed reimbursement and stated its opinion that the assays are still investigational, while the Southern California Oncology Association (which has had a vastly greater experience with the clinical use of these assays over the past 6 years) came out in strong support of reimbursement. There was again vigorous debate, but the final decision was again unanimous -- this time a 20 to 0 vote in favor of reimbursement.

The official Blue Shield of California conclusion is stated (verbatim) as follows:

'Drug resistance testing in oncology is accurate and reliable. This information can affect clinical decision making and can lead to the avoidance of ineffective and potentially harmful chemotherapeutic agents. Although there are few prospective clinical trials comparing standard therapy with chemotherapy chosen by in vitro assay, there are sufficient published data to determine their safety, clinical utility, and impact on clinical decision making.

RECOMMENDATION: It is recommended that the human tumor drug resistance assay is eligible for coverage when this information is required for the selection of chemotherapy.'

On October 15, 1997, the issue was considered for a second time by the nationally-respected California Blue Shield Medical Policy and Technology Assessment Committee.

In the period between 1994 and 1997, additional questions had been raised. These included negative reviews by the National Blue Cross/Blue Shield Association (with the senior author of the review being Dr. Naomi Aronson, who was also the senior author of the identical review essentially just recycled and published in the September, 2004 J Clin Oncol review, with the same recommendation against coverage, as no additional studies meeting Aronson's curiously unprecedented criteria had been published to review in the interim), by the American Medical Association, and two negative editorials authored by Dr. Maurie Markman of the Cleveland Clinic, in conjunction with a physician employee of the Aetna Insurance Company. Thus, the entire issue was re-opened for scrutiny and re-consideration.

An outside consultant from the University of California San Francisco did an ostensibly thorough examination of the issue. He prepared a detailed report, recommending against considering CCDRT a reimbursable, non-investigational service.

What is different about the California Blue Shield review, compared to the other reviews, is that California Blue Shield invites input from all affected parties, publishes preliminary conclusions and recommendations, and then holds an open hearing, where all points of view can be considered. It is a fact that, prior to obtaining input from proponents of

CCDRT and carefully hearing both sides of the issue in a back and forth presentation of points of view and open debate, the Medical Directors of California Blue Shield were pre-disposed to change their policy. However, upon consideration of all points of view and due consideration of all arguments and counter-arguments, the expert technology assessment panel, including the Blue Shield Medical Directors, unanimously voted against their UCSF consultant, against the findings of the National Blue Shield technology assessment, in favor of continuing the policy of considering CCDRT to be a fully-reimbursable, non-investigational service.

This was and continues to be a very important event. There is no question that the California Blue Shield committee did the only thing that it could do, when faced with all points of view and when forced to examine all evidence in an objective and impartial manner. There is also no question that this outcome will be repeated in future cases that go to arbitration or other legal procedures.

Moving to consider the two day national Medicare Coverage Advisory Committee ("MCAC") review in November, 1999:

During the session on November 15-16, MCAC's laboratory and diagnostic services panel heard presentations from experts regarding the clinical data associated with the human tumor assay systems. The panel listened to formal presentations from the NCI, the FDA, ASCO, representatives from various laboratories which provided the tests, outside physicians, and patients. The panel questioned presenters carefully on clinical performance, study findings, literature analyses, and patient impact of the tests.

After considering the evidence, the panel concluded that the tests demonstrated clinical utility for directing therapy for chronic lymphocytic leukemia and showed promise in directing therapy for other types of cancer. It should be noted that the MCAC was specifically instructed NOT to make a coverage recommendation, but was instructed simply to have an open discussion upon hearing all of the evidence and to offer individual opinions, which were to be considered by Medicare. The entire proceedings of the two day conference were recorded and transcribed verbatim and are available on the Web.

The following are verbatim quotes, taken from the official US government transcripts of the Medicare Coverage Advisory Committee meeting on Human Tumor Assays, held in Baltimore, MD, November 15 and 16, 1999. I have tried to find and present quotations which best summarize the feelings and opinions of each of the committee members, after hearing pro and con presentations by both proponents and critics, including the laboratories, representative oncologists (and a patient) familiar with the assays, the FDA, American Society for Clinical Oncology (ASCO), the NCI, HCFA itself, and two outside consultants.

Each of the Committee members introduces herself or himself, followed by the verbatim quotations.

MS. SIMMERS: I am Lisa Simmers. I'm from Bridgewater, Virginia. I am currently a health care administrator, and am here in the interest of the laboratory community, I guess.

MS. SIMMERS: I think this fits into the category of the tools that a physician should use in order to dose, or what course of treatment to endeavor and to go in that dialogue between the patient and the physician and the family. I think the one presenter and one panel member pointed out something that I think about all the time, at least in one region, and I think it unfair to have Medicare beneficiaries pay their insurance premium and not get access to that test. So I'm very much the 35,000 foot view of the Medicare beneficiaries' needs and how well what we decide to recommend would serve those beneficiaries. And I think Dr. Bagley's point about they help pay for it is very valid. They do help pay for it, and as insurance carriers are paid, I think the same level of access should be available to Medicare beneficiaries that there are provided for those who have private insurance.

I have some concerns, however. Certainly the accessibility of the test, although I am convinced there are ways to address that, I think there would be a duty to promote this as, promote its accessibility not only in very small regional areas, but nationwide, should we decide to cover it. I think there are some valid research and scientific questions to be answered. I do believe that this is a diagnostic test and should be held to that criteria, and not to that of therapy. I think that was clear, and although I think the science could be better, it's not a perfect world, and what we see is at least compelling evidence to continue.

The policy specific issues, certainly I am not the expert in that area, but it does seem to be available to us to look at those cancers and what circumstances with what drugs are best pursued under this coverage recommendation, should we make it. It seems to me the processes are in place to do that, so I don't fear that it can't be done. And certainly, the devil will be in the details of that kind of process.

But after everyone has said their piece, I guess if any of us in this room were to face the terrible news from our clinician tomorrow that we had cancer, who among us would say no, this assay is not for me. And I believe if it's for us, it is for Medicare beneficiaries as well. So that's my comment.

DR. SUNDWALL: I'm David Sundwall. I'm a physician and I'm president of the American Clinical Laboratory Association, in Washington, D.C.

DR. SUNDWALL: Thank you. I feel fortunate going at the end of this discussion, so I get the benefit of all these experts, and I don't mean to be flip about that. I really appreciate the expertise of the panel, more analytical than those of you who carefully reviewed the studies. My perspective is that of a family physician like Paul, who is taking care of patients, diagnosed cancer, followed them through chemotherapy, and seen sometimes the benefits, more often the heartache and morbidity that's associated with that. That doesn't mean I'm not a believer, it's just that I think we need to have a very healthy skepticism about current cancer treatments.

I am also coming at it from the perspective of someone who's spent most of my adult life in health policy here in Washington in different capacities, and I'm very familiar with the tension between those advocating something new and wonderful, and the payers who in their responsibility to monitor how we spend our funds, make sure they are done appropriately.

However, I must admit that through the course of the discussion yesterday, I was reminded of a quip I once heard about economists, which was intended to be funny, but the economists were described as people who, when something is proven to work in practice they want to find out if it works in theory. And it seemed to me the preponderance of evidence was that this is in fact a useful tool, it's information, I think in some respects it has been oversold in what it promises, but I look at it more simply as Grant described, it's information. And it clearly would be useful to me and my patients in making decisions about chemotherapy. I think to put it in context of reasonable and necessary is wise. It is reasonable. Whether it is necessary, I think must be left to the discretion of those experts who are going to be using it. The last comment I would just make is, I think from a health policy standpoint, we keep talking about quality access and costs, and access I think is important, and this is a useful technology and ought to be accessible to Medicare beneficiaries appropriately applied. I do think the cost issue is promising. I was disturbed by the testimony of the [American Society of Clinical Oncology] clinical oncologist yesterday. It seemed very self serving. We're neutral, but by the way, cover chemotherapy, and don't you dare tell us what we can't use. And I really thought that was not constructive, and I think it's troublesome.

DR. KLEE: I am George Klee. I am from Rochester, Minnesota, and I'm a clinical pathologist.

[Note: Dr. Klee's detailed statements showed that he was misled by the presentations by HCFA's Dr. Burken, who had showed multiple slides of studies of assay technologies which had been abandoned in the mid-80s and which were not among the technologies being considered for Medicare reimbursement.]

[The following is a direct quote from the Committee Chairman, Dr. Ferguson, concerning HCFA's presentations:

"So I am not certain that the protagonists were given all the critique information. We didn't have it...I think that that could be done a little bit better in the sense that if all the critiques of presented papers could be given to the presenters in advance, they might have time to prepare some rebuttal and response to the critiques.]

[So, based on his incorrect understanding of the literature, Dr. Klee made the following motion:]

I move that the advisory committee recommend that there is not sufficient scientific evidence to demonstrate the clinical utility of HTASs in selecting appropriate cancer chemotherapy.

[vote was 8 - 1 against the motion, with two abstentions; abstaining were Drs Mintz and Brooks, in favor was Dr. Klee, the rest voted against the motion.]

DR. FISCHER: Paul Fischer. I'm a family physician from Augusta, Georgia.

The question is whether Medicare should pay for it given what we know about it at this point in time and you know, I think the data is pretty persuasive. I am hopeful that that will change the practice of oncology, because I see a very different part of that practice than what the average oncologist does. And they're the patients and their family who have failed chemotherapy with very terrible results. And I just want to repeat this one more time. In the total practice, in my total practice, there has been as much harm as benefit from oncology.

DR. BROOKS: John Brooks. I am chairman of pathology and laboratory medicine at Roswell Park Cancer Institute.

DR. BROOKS: As a pathologist, I certainly came to this without much knowledge or interest, in a sense of one who would give chemotherapeutic drugs, and kind of evaluated it in the same way as I would evaluate any new upcoming test that we have actually to evaluate, almost every week I would say, in the clinical laboratories. As a pathologist, generally, my thought would be that we like to see more tests done and certainly, useful tests are very helpful to people. So you know, in evaluating the information that I got beforehand and that we heard here, I was certainly impressed with how much had been done. I was actually a little bit surprised at how much had not been done, however. I mean, in some settings, it certainly seems to me like the data is there for utility. I am not doubting that the test, I mean it's been mentioned before by a number of people that, you know, I actually believe that the test does test resistance and so forth, and that we may have to decide which of the tests might be recommended, or maybe two tests, A and B, whatever, but histology specific type of data wasn't necessarily there, except in certain situations.

MR. BARNES: Rod Barnes. I am the industry rep on the panel. I work for AlCon Labs in Fort Worth, Texas.

I was sitting here thinking that there are a number of small companies or even very small labs who can't quite present the randomized clinical trial that many of us would like to see, the conclusive once and all for cause and effect, RCT. But they do seem to present a good mass of evidence suggesting patient benefit, as has been mentioned, and I certainly, if I personally or someone in my family was involved, I would like them to have access to this test.

DR. FERGUSON: I am John Ferguson. I am a practicing neurologist, and I have just retired from the NIH, where I directed the consensus development program for the last 11 years.

I was impressed with some of the leukemic studies and some others that there is some usefulness and that it needs to be mined, but mined carefully and under the right conditions.

Just another comment about randomized trials. Where I sat at the NIH as chair of the technology assessment committee for the American Academy of Neurology for a number of years, the number of randomized trials with outcome measurements for diagnostic tests, I don't believe I could have counted on one hand. I would have to look very hard to find those tests. I remember seeing reference to one or two, but -- and there may be more, but I think there is no question that for diagnostic tests, randomized trials with good clinical outcomes are extremely rare and I believe that, however, they should be done. We need better standards.

DR. MURRAY: I'm Robert Murray, a clinical biochemist in practice in Chicago, Illinois. Spending my life generally in the laboratory, I tend to analogize all of the situations, the questions, to existing laboratory tests. There is no question that many laboratory tests which are routinely approved currently have nowhere near the evidence, nowhere near the accuracy and predictive value that the tests that we're considering today, that we heard about yesterday, have already demonstrated. Yes, we do have to look at outcomes. We have to look at outcomes measured in different ways. We have to look at evidence. But the evidence, even if the bar is raised higher, the evidence that we have heard certainly exceeds the evidence that we have for many, many tests currently in use.

DR. LOY: I'm Bryan Loy. I am with the Kentucky Medicare carrier. I represent the Medicare system at the state carrier level.

I have a couple of comments, first of all regarding the presentations. I noticed a number of cancers were being elaborated on. I am still not clear at what point in the clinical progression of the disease, or how often the testing should take place. However, having said that, this does sound like this is a tool that be could be very useful. But having listened to the presentations yesterday, again, we were focusing on specific cancers, and to try to take that tool and apply it to all cancers at this point in all clinical scenarios, doesn't seem to be quite reasonable at this point. We really didn't talk a lot about the sarcomas, or trying to talk about such broad fields as hematopoietic neoplasms. I think at least in my mind, I would need some more convincing evidence to try to apply this technology wide spread, and I think that this is certainly germane to a policy type discussion. The other piece that's still lacking in my mind is where this really fits clinically. Because some cancers are clearly curable with chemotherapy, or they're curable with radiation therapy in combination with chemotherapy, or they're curable with surgical resection, or any of those combinations. And trying to really fit this into that niche is going to be quite difficult to do from a policy perspective. Having said that, I think that there certainly is some promise. I think there is some utility that has been potentially demonstrated here, but I am not clear on where this fits yet.

MS. SNOW: I am Kate Snow. I am the consumer rep on this panel, and I am the director of senior services for Northern Michigan Regional Health Service, and I am an advanced practice nurse in gerontology.

I believe that if I were a cancer victim, I would want this study available for my use. I would feel it was reasonable and I would also very much feel it was necessary. Listening to the quality of life and the cost of life that could be gained, and to decrease the burdens for individuals was also very compelling. If it takes the guess out of the therapy that's used, I think it's a very good tool to have available to us.

I struggle with whether or not this test will be available in a way where those of us in northern rural Michigan will have access to this kind of tool or not, and what that might look like in the future.

DR. KASS: I am Mary Kass. I am chairman of pathology at Washington Hospital Center, and director of integrated laboratory services for MedStar Health.

First of all, I think my first question was about the testing methodology, but I think that there is overwhelming evidence to show that these tests meet all the normal QC, all of the normal standards that all other laboratory tests have to meet. I think that they're valid, I think that they are reproducible, so the third generation of tests for me is no longer a concern in that respect.

The question has been raised about necessary versus clinical utility. I don't know how to define a necessary laboratory test; I think that's really in the mind of the user. When I was in training, which wasn't all that long ago, the emergency room of a downtown urban hospital in Washington, D.C. didn't even have a laboratory open from midnight until eight a.m. because there were no laboratory tests that were necessary to make clinical diagnoses. But we've come a long way since then, and I think medicine has grown and realized that there are many things that can help physicians do a better job in taking care of their patients. So the clinical utility of this test, I think has been demonstrated, to certainly my satisfaction. The fact that the test is difficult to do because you have to acquire fresh tissue, it has to be shipped in a certain way quickly to a laboratory, that doesn't bother me either. That doesn't change its utility. I remember when we first started doing flow cytometry, the transport of specimens to do flow cytometry on was a big challenge to us. Now we do it routinely and we don't lose specimens in the transport process. It is very intriguing to me that this particular methodology may be very helpful in evaluating new drugs, the number of new chemotherapeutic agents that are rapidly being introduced to try to help us have a greater impact to the treatment of cancer. I think that anything that we could use to help define which modalities have a greater possibility of working and which don't, would be very helpful. I think it also allows the earlier consideration of other treatment modalities for patients, rather than going through a whole course of chemotherapy and waiting for the end point of no response. Earlier in the course of that, a clinician may have an opportunity to switch a chemotherapeutic drug, or remove one which has a very toxic side effect from the treatment regimen.

I guess in summation, I think that we haven't done a terrific job in treating most of the solid tumors. I think everyone is very disappointed in the fact that we haven't been able to have greater success than we have. I think that this is another tool, one of many, that could be available to clinicians that might help, certainly in terms of the quality of life, if we could remove drugs from the treatment regimen that were not effective, and perhaps in a better outcome. I think the patient that testified yesterday, that's one case, it's anecdotal. However, I've practiced pathology for 32 years; I have never seen a patient with widely disseminated pancreatic carcinoma that survived. You have to take notice of that. I think that's worth listening to.

DR. HAUSNER: I am Richard Hausner. I am a pathologist practicing in Houston, Texas. DR. HAUSNER: For me, I would like to take the approach to try and put my comments in the context of my own clinical experience, my own day-to-day, I'm a working pathologist, although I am on the active clinical faculty of Baylor College of Medicine and the University of Texas Health Science Center in Houston. I practice in a community hospital, but I have very long reach in terms of my clinical experience. I have a big practice. And I can tell you that in Houston, Texas, where there is quite a bit of health care going on on a daily basis, not once ever in my life, with all of the cancer patients that I've seen, have I once been asked to harvest tissue for this procedure. Not ever. And I can tell you that if any of the patients in my practice had had this testing, that we would have been involved in the harvesting by definition, because the surgeons would have surely asked. So I know that it hasn't happened.

Nevertheless -- and I came in here reading the source material with that bias, because I had that bias from the very beginning. But nevertheless, somewhere around the middle of yesterday afternoon, my thoughts began to crystallize, and they crystallized during the time that, in the afternoon session when the data was put up to a tremendous amount of scrutiny and a very sophisticated critique, and I thought that it held up pretty darned well. And I have come to the conclusion that while over the past 20 years of the research that has developed for this technique, it clearly was a research tool and not ready for prime time, that the decision was correct not to allow this into Medicare's realm and therefore, give it the validity to go forward. Because what is someone's exciting front line technique comes very close to someone else's quackery, and at some point it would have been premature to allow this. But I believe now that the third generation technologies clearly take this beyond a research tool and that from this point forward, I would hope that the clinical studies will be conducted to refine where this could be best used.

Another analogy would be that a, that if this technique is not permitted in its current state, then the panel ought to reconvene and consider removing microbiologic sensitivity testing from the armamentarium of physicians, if this is not approved. The truth, I believe, lies somewhere in the middle, therefore, and just like so many other things we do in medicine, that this is a useful tool, imperfect as it is, and the ground rules may have to be carefully defined, but to turn the test away in its entirety, I believe would be inappropriate.

And in closing, I would point to the final paragraph of Dr. Weisenthal's paper in which he talked about whether we use the civil or criminal criteria of preponderance of evidence

versus beyond a reasonable doubt. Beyond a reasonable doubt, we don't have. Preponderance of evidence, I believe we do. And therefore, my conclusion is, as a rough sketch, is that something ought to be done towards bringing this test into, as another tool for physicians to use.

MS. KRAFT: I am Cheryl Kraft, administrative director of laboratory services, Minneapolis.

I think, again, this laboratory test is a tool for a physician. The physician should take advantage of all the tools available to him to treat a patient. And since studies show that only 25 to 30 percent, again, of patients do respond to the test and/or the drugs and/or the correlation of the drugs and the chemotherapy that we have available to them, should we not consider, due consideration to looking at the advantage of these human tissue assay tests and the resistance that has been found to chemotherapy drugs? So one concern of mine is that they, in defining what they're going to reimburse, that they contact some of the scientists and physicians in the audience that are doing this research, that they find out what is the cost of producing the test and get some real life cost data, so when they set what they are going to pay the physicians for doing these tests, that they have realistic up to date direct costs.

DR. HELZLSOUER: I'm Kathy Helzlsouer, oncologist and professor of epidemiology at Johns Hopkins School of Public Health.

...although there's a correlation with survivors, it's the problem we always have with reviewing issues, that responders always do better than non-responders, and it's probably a good marker for responders. But I think we have to see how we can clinically use that in either choosing chemotherapy, and I think the compelling argument is the issue of avoiding unnecessary chemotherapy, but I'm not sure I have the evidence to say that would actually be done in practice.

I think it should guide but not dictate care. I don't think we can use the test to dictate care, and there would be lots of reasons in addition to the fact that you might have a situation, since 20 percent would respond even if they were resistant on this assay, according to the literature we have, and that's based on sensitivity response. You could have a situation where somebody, you still have a 20 percent chance, and in combination you might choose a less toxic drug rather than a more toxic to which they are sensitive, because you're using it in combination. There are a variety of scenarios you can come up with that this test alone should not be your sole, to dictate therapy alone, and there has to be a combination of other factors along with this test result.

DR. MINTZ: I am Paul Mintz. I direct the clinical laboratories and blood bank at the University of Virginia Health System, where I'm a professor of pathology and medicine. DR. MINTZ: My concerns have been already stated by others, but I want to use this opportunity to state that I think the sense of the committee was best expressed in motion number three, and that these tests show promise for clinical utility, and that motion deliberately did not state, distinguish between sensitivity and resistance testing, so I think

the sense of the committee reflects that it is supportive of both sets of testing. And I would only add that I also hope the coverage is adequate to permit this technology to be used."

Now, following this meeting, Medicare decided to make no National Coverage Decisions but, instead, to make the transcripts available to assist in Local Coverage Decisions. It is completely false to state or imply that there exist any national coverage decisions which are unfavorable regarding the technologies currently available here in California, which were the main technologies which were the subject of the MCAC and California Blue Shield reviews discussed above.

Subsequently, a paid representative of Oncotech was able to arrange for closed and unannounced meetings with the Southern California contractor (TransAmerica, I believe) and successfully (from Oncotech's point of view) drew an entirely artificial distinction between "resistance" and "sensitivity" testing (I am happy to discuss the entirely arcane and artificial distinctions upon request).

Based on the generally favorable MCAC reviews (the technologies most favorably reviewed, by the way, were the cell death/apoptotic endpoints) and based on a prior favorable Administrative Law Judge decision, a Local Coverage Decision was made to cover "resistance" testing, while denying coverage of "sensitivity" testing. When I read of this in the monthly Medicare newsletter, I requested and was granted meetings. I pointed out that I had also received a favorable Administrative Law Judge decision mandating payment for a large number of outstanding claims (payment which was made) and presented the data relating to the predictive accuracy of my cell death/apoptosis technologies and pointed out how the most favorable aspects of the MCAC review had pertained to these technologies. Subsequently, I was granted a favorable local coverage decision on a basis identical to that of Oncotech, as described in a subsequent Medicare monthly newsletter (see page 31):

[http://www.medicarenhic.com/news/provider\\_news/ca\\_mbr\\_archive/newsletter\\_110.pdf](http://www.medicarenhic.com/news/provider_news/ca_mbr_archive/newsletter_110.pdf)

Which states:

"One type of extreme chemotherapy resistance (ECR) assay measuring radiolabeled thymidine incorporation into tumor cells exposed to antineoplastic agents was described (and coding instructions given) in the September 2000 edition of Your Medicare Newsletter (#109). That technology and the codes remain unchanged.

A slightly different form of tumor cell resistance assay consists of exposing tumor cells to antineoplastic agents and performing at least one or more of the following three cell death endpoint tests to determine tumor cell survival: 1) Differential cell staining and microscopic counting; 2) microplating and use of coloring reagent MTT (Dimethyl thiazol-diphenyltetrazolium/thiazolyl blue); and 3) measuring ATP content.

This test will be covered for the same tumors as extreme chemotherapy resistance: chronic lymphocytic leukemia and solid tumors including ovarian, breast, lung, and colon. To bill for this type of chemotherapy resistance use the miscellaneous immunology CPT code 86849 and include the words "cell culture tumor resistance" in Box 19 of the paper claim form, or the "Comments" area of electronic billing. All conditions that apply to the extreme chemotherapy resistance assay in the September 2000 article also apply to this form of tumor resistance assay. Cell culture tumor resistance testing (for preventing use of known anticancer drugs that are not likely effective in this specific tumor) is currently considered different from human tumor cell sensitivity assays (which try to determine specific drug and dose effectiveness). The Carrier does not cover tumor cell sensitivity assays at this time. "

Now, as noted above, the distinction between "sensitivity" and "resistance" is more semantic than substantive, but the key issues remain the following:

1. In virtually all forms of cancer, clinical trials have failed to identify "best" drug regimens for use in individuals with given forms of cancer.
2. In the absence of clear guidance from clinical trials, oncologists have been documented to use reimbursement (payment to the oncologist) as the most important criterion for selecting between the large array of otherwise equally acceptable regimens. This costs the health care system vastly more than the relatively modest costs of laboratory tests to match treatment to tumor in a biologically relevant and profit irrelevant manner.
3. The established criterion on which to judge laboratory tests used to help in the selection of cancer treatment is test accuracy and not test efficacy (which is an unprecedented criterion never before applied and currently not being applied to any other tests used to help in the selection of cancer treatment).
4. Cell culture tests with cell death endpoints have been exceedingly and reproducibly well established to be usefully accurate in correlating with and predicting for clinical outcomes, including tumor response and patient survival.
5. ASCO and Blue Cross TEC reviews were closed and opaque and did not solicit or allow commentary from outside the closed review panels. These were not new reviews, but simply recycled/repackaged versions of prior reviews (in the case of Blue Cross TEC by the same senior author) published in the 1990s.

These reviews specifically excluded from consideration all data pertaining to the accuracy of the cell culture tests and included only small, poorly-controlled studies of test "efficacy" which were utterly inadequate to address the question of whether or not use of the tests improves clinical outcomes (again, an unprecedented criterion for evaluating such tests and a criteria which is being applied nowhere else in cancer medicine).

6. California Blue Shield and National Medicare performed comprehensive reviews which were "open" affairs, including commentary, debate, arguments for a wide range of

out outside experts. These reviews included consideration of the established criteria of test accuracy and these reviews were certainly supportive of at least selective utilization of these assays in cancer medicine.

7. There is no national Medicare coverage policy pertaining to any of the laboratory technologies currently available through California laboratories. Medicare has specifically made coverage of these technologies a local decision, on the grounds that the considerations are complex and the local contractors are best suited to communicate with the local providers and understand their services.

8. The local Southern California Medicare contractor previously reviewed the available information and made the decision to provide partial coverage. There are no new data which have emerged since this decision which should prompt a decision for global non-coverage. All that has emerged is a repackaging of old data and old and invalid arguments against coverage by Dr. Aronson's long opposed Chicago TEC review group and by an ASCO panel comprised of three former researchers with a technology discredited twenty years ago (Von Hoff, Hamburger, and Hanauske), no researchers in the technologies currently being applied, two researchers (Schrag and Burstein) actively promoting "molecular" assays which are supported with absolutely no data relating to assay "efficacy" and with much less data relating to assay accuracy than exist to support the application of the cell culture assays. The ASCO panel also represents an organization which has been zealous in its support of an inherently corrupt system which won't allow drugs to be chosen on the basis of tumor biology but instead protects the ability of ASCO members to choose drugs largely on the basis of profit margin or least inconvenience to research clinics.

In short, there is no objective justification for eliminating a reimbursement system which at least partially supports the utilization of IVCA in cancer medicine and there is much justification for expanding this reimbursement system to promote even greater utilization and development of laboratory-based mechanisms for improving the match between tumors and an ever-increasing number of partially effective and horrendously expensive drug therapies.

Sincerely yours,

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