THE CANCER LETTER

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NCI Rethinks Cancer Center Grants

By Paul Goldberg

NCI is moving toward adopting a formula that will fundamentally restructure the manner in which cancer centers are funded.

The new approach, developed by a working group of the National Cancer Advisory Board, seeks to eliminate the advantage that comes with a center's longevity in the program.

As it stands, just being in the centers program for many cycles can build up an institution's funding base. This favors older centers.

(Continued to page 2)

News Analysis

Robert Cook-Deegan's Viewers' Guide To the Super Bowl of Gene Patent Cases

Patent litigation is a blood sport if you see corporations as people and count spilled ink or loss of money as hemorrhage.

One of the most closely watched cases in recent years centers on genetic testing for BRCA1 and BRCA2 genes.

(Continued to page 10)

NCI Seeks to Eliminate Inequity In Cancer Centers Funding

(Continued from page 1)

Two years ago, smaller and emerging cancer centers asked the institute to restructure this mechanism two years ago, and NCAB formed an ad hoc working group to consider alternative formulas for funding.

The group was headed by William Hait, global head of research and development at Janssen, a unit of Johnson & Johnson. The working group included top officials from a broad range of centers; large and small, established and emerging.

At the meeting Feb. 27, NCAB was asked to comment on the proposed formula, which is now being finalized by NCI staff.

The group recommended that the Cancer Center Support Grants be comprised of these components:

• **Base award:** At renewal, a predetermined base award applicable to all centers of the same type would be the starting point. All basic centers would receive one level of money, then all clinical centers, and then all comprehensive centers. This component would use up 50 percent of the direct cost budget of the NCI Centers Program.

• **Merit funding:** This would be calculated on a linear scale as a percent multiplier of base award, using impact score. If a center is underperforming, it may end up with a reduction of its base award. This component would use up 30 percent of the direct cost budget of the centers program.

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• **Size:** This would be calculated as a percent multiplier of the base award, using figures for total peer-reviewed funding reported by the center. This component would use up to 15 percent of the direct cost budget.

• **Supplements:** This would be based on review of proposed innovative and impactful programs, cores, new initiatives and consistency with NCI priorities. This would use up to 5 percent of the program's budget.

At the NCAB meeting, NCI Director Harold Varmus said he likes the new formula, because it allows de novo consideration of each of the centers' budgets, eliminating the advantages of longevity.

"The great thing about the supplements is that it doesn't go into the base," Varmus said. "I'm a huge of supporter of this, and I think 5 percent is a lot of money. I'd also point out that we could use this mechanism not just for the NCI-designated cancer centers, but also for other NCI-supported institutions that get money, for example for our NCORP [NCI Community Oncology Research Program] web of centers and clinical trials."

Also, the approach makes it easier to reduce funding for centers that aren't performing.

Varmus also said that when NCAB reviews the proposal for the funding formula, it would also have the opportunity to recommend increasing the aggregate funding received by the centers program—and pinpoint other areas of NCI spending that could be reduced.

"I think some of the question that the NCAB might want to think about and take up at the next meeting, is whether you want to endorse the idea of an increase, and whether an increase in the cancer center budget comes out of other budgets," Varmus said.

"To make a significant change would be pretty expensive. Before saying these are the pride of the world—or the envy of the world, and the pride of the U.S.—and we need more money for them, it would be very useful to think about what the [Cancer Center Support Grant] money goes to.

"After all, there are many other ways in which we support cancer research at these institutions, not the least of which is grants and [Specialized Programs of Research Excellence] and P01s, and everything else. I think it would be very useful to say what would happen if we were to increase the cancer center budget overall by 1 percent, 5 percent, 50 percent, 100 percent?

"Does that make sense? It's hard for you to gauge what the likely impact is, because it would be up to us to decide if we went along with some recommendation from the NCAB about the overall center's budget. Where would reductions be taken? That's not an easy question

these days."

The advisory group was asked to discuss the funding change proposal. A more complete version will be sent to the group at a later date. The working group's version of the proposal was more detailed than the version that was presented to the Board of Scientific Advisors last June (The Cancer Letter, July 3, 2013).

Discussion of the problem started in April 2012, when NCI announced a plan to cap the growth of awards to cancer centers while also tightening the requirements for review (The Cancer Letter, May 11, 2012).

Recommendation #1

- Base award
  - should vary by Center type (basic, clinical, comprehensive), based on CCSG requirements (50%[1.])
  - at renewal, a predetermined base award applicable to all Centers of same type should be starting point.
- Merit funding
  - calculated on a linear scale as a percent multiplier of base award, using impact score (30%[1.])
    - Impact scores of low merit may result in reduction of the base award
- Size
  - calculated as a percent multiplier of base award, using figure for total peer-reviewed funding reported by the center (15%[1.])
- [Supplements]
  - based on review of proposed highly innovative and impactful programs, cores, new initiatives, and consistency with NCI priorities (5%[1.])]

[1.] Refers to direct cost budget of the Centers Program; not individual CCSG grant award.

Kevin Cullen, director of the University of Maryland Greenebaum Cancer Center, objected to the funding restrictions in a letter to Linda Weiss, director of the NCI Office of Cancer Centers. Separately, a group of 11 center directors expressed similar objections in a letter to Weiss.

"I believe that the current proposal effectively legislates an inequitable system, which is largely based on history, and effectively excludes consideration of a change in populations and demographics or changing national needs in future times," Cullen wrote at the time.

NCI responded by setting up a 10-member committee that produced the current report.

The Anatomy of Historical Inequity

Top-level NCI officials appear to have accepted the rationale for changing the formula for funding centers.

At the March 12 meeting of the Clinical Trials and Translational Research Advisory Committee, James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis, offered the following synopsis of historical inequity that occurred in the centers program:

"You could say 'how did that happen?'

"What happens is that centers come in every five years. As you are probably too well aware, there are ups and downs in NCI funding levels. There's no question if you look historically, if you've been historically fortunate to have your grant renewed at times when the budget was going up, there were times when institutions got substantially greater than the mean increases in funding.

"And at the same time, there have clearly been times when grants got essentially no increase in funding despite extraordinary review scores because funding levels were low.

"And over a series of funding cycles, if you were continuously unlucky, and that has happened to many different centers, especially if you started out as not one of the initially large centers that had large levels of funding, one could end up with an extraordinarily high base of NCI related funding and a core grant with either direct or total cost that was not commensurate with the activity going on at that center.

"A subcommittee of the cancer center directors has been working for over a year to try and figure out different models that might improve the disequilibrium in funding over time and it has as you might have guessed been an exceptionally difficult job.

"I think the work that was done by those individuals was exceptional, not only because it happened at all, but because it called for some evening out of funding, that is, funding going down, at the highly funded institutions and funding going up at those who were less well funded.

"And getting those to sit around the table and actually come together and agree that some change in the equity and the distribution of the funds is remarkable event. The modeling that's been done is

not complete, and there is no final decision about how such a model should be implemented. I thought it represented a degree of selflessness from the individuals who were involved in developing a response to this historical inequity that was quite remarkable."

NCAB Discusses the Proposal

Since changes in funding of the cancer centers will likely produce profound changes, NCAB discussion of the proposal warrants attention. A partial transcript of discussion appears below.

HYPOTHETICAL FUNDING CALCULATION USING BASE AWARD + MULTIPLIERS FOR MERIT AND SIZE (FOR EXAMPLE PURPOSES ONLY, ALL FIGURES IN DIRECT COSTS)

Center Type	Basic (7)	Clinical (20)	Comprehensive (41)
Base Award	$850,000	$1,050,000	$1,250,000
Maximum Merit Award (percent multiplier of base award, declines linearly with increasing impact score)	$1,844,500	$2,278,500	$2,712,500
Maximum Size Award (percent multiplier of base award, using quintile of peer-reviewed funding)	$782,000	$966,000	$1,050,000
Maximum possible award	$3,476,500	$4,294,500	$5,012,500

Hait's presentation slides are available on the NCI website.

TYLER JACKS [NCAB chair, director of the Koch Institute for Integrative Cancer Research, and the David H. Koch Professor of Biology at the Massachusetts Institute of Technology]**:** I actually want to start with respect to the non-renewal question, which you brought up early, but didn't really come back to, I'm just curious what your group was thinking toward the end of your deliberations.

HAIT: It's a sticky wicket, if you will.

There are many, many issues for why the NCI would want a center in a particular geographic location, and I think that if there are ideas to work with those centers to help them improve, there's that hope.

But for chronic underperformers, where there's not another important aspect to them, the group didn't feel that we had the imprimatur to make such a strong recommendation, but at least bring it to the attention of the NCAB.

CHARLES SAWYERS [chairman of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center, Investigator at Howard Hughes Medical Institute, and professor of medicine at Weill-Cornell Medical College]**:** I was captivated by one of the early conclusions, which was to reward the cancer centers for what they're good at and not penalize them for what they're not good at.

Could you say more about what that actually means in terms of implementation, because I have the impression there's the checklist of things that you need to meet.

Does this mean modifying some of the guidelines to qualify as a cancer center?

HAIT: I think, broadly, the way I understood it—and actually, the recommendation came from your center, which is quite interesting—that broadly speaking there are certain components that make up a comprehensive center and they can change.

But within those components, the CCSG can't possibly fund everything. You can't possibly do everything.

So, really, the focus and the emphasis is on what you're doing and how well you're doing it, and, most importantly, the impact of the science that's coming out of your center. So that was the genesis, and that was the thinking behind that.

SAWYERS: Does that result in an action item that comes back here?

HAIT: It might. Linda [Weiss]'s group will take that recommendation back and see how perhaps the reviews might be tweaked but we didn't go that far.

MACK ROACH [professor of radiation oncology and urology, and chair of the Department of Radiation Oncology at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center]**:** It's a little unclear to me how you balance the need to have the equitable distribution of cancer centers and meet the needs of the various diverse populations at the same time, when a center is underperforming.

If you eliminate funding for that center, you may exacerbate those pre-existing issues and make those situations worse. I'm not sure how you would metric that—and the correlation coefficient that you showed when you brought the curves closer to the line, the question is, does that adversely impact all those other considerations that you mentioned?

HAIT: I think you're hitting right on the complexity of the problem—how you balance a mandate to ensure access to the kinds of quality of research and translational research, to geographic areas, to special populations, to the underserved—that's why it's something that should be looked at. I'd ask Harold to comment here.

It's a complicated issue.

VARMUS: The dilemma here is a classic one. Would you be better off giving your money to people who are underperforming so they can perform better?

I think, historically, that hasn't been the solution to the problem. I would rather see the money go to the places that are performing best. It is a dilemma.

Obviously, we take into consideration making all these decisions—where are the centers located, what are the populations its serving, what kinds of research it does.

What I think is really good about how this report has been generated is it is generic.

It leaves to us the flexibility to make adjustments based on other considerations, through supplements and other kinds of qualifications. I think it's important there wasn't a directive in our plan to close a center. Obviously it is possible for a center to lose its designation, but we're not asking for that prescription.

It's an enormous labor, preparing an application for a cancer center.

Having been a cancer center director myself, I know the amount of paperwork even for a non-competitive renewal, let alone a competitive renewal, is tremendously taxing on the system.

That's a separate problem that I think is one we should pay attention to once we get to the point of knowing what the criteria are going to be. I think that will help shape the application process.

WILLIAM SELLERS [vice president and global head of oncology for Novartis Institutes for BioMedical Research Inc.]**:** Thanks for doing this.

I know it's not a very thankful position you're in. I'm not going to make it that easy. The statement I made at the primary meeting I was that I think the budget for the cancer centers is too low. I understand that we're in a tight budget situation, but it doesn't matter to me.

We need to increase funding for the cancer center program in general—so we're not spreading tiny bits of money around to 68 cancer centers to the point where they become ineffective in getting anything done.

I think my own feeling is personal. Tough decisions need to be made to find greater resources for the cancer center program in general.

The question I have is about the effort to match merit and payments, and it seems to me that it assumes

NCAB Cancer Centers Working Group Members

Chair **William Hait**, global head for pharmaceutical research & development at Johnson & Johnson

Frederick Appelbaum, executive vice president and deputy director at Fred Hutchinson Cancer Research Center

Mary Beckerle, CEO of University of Utah Huntsman Cancer Institute

Kevin Cullen, director of the University of Maryland Greenebaum Cancer Center

Chi Dang, director of the University of Pennsylvania Abramson Cancer Center

Stanton Gerson, director of the Case Western Reserve University Case Comprehensive Cancer Center

Michelle Le Beau, director of the University of Chicago Comprehensive Cancer Center

Craig Thompson, president and CEO of Memorial Sloan-Kettering Cancer Center

Kristiina Vuori, president, interim CEO, and director of Sanford-Burnham Medical Research Institute

George Weiner, director of the University of Iowa Holden Comprehensive Cancer Center

Executive Secretary **Linda Weiss**, director of the NCI Office of Cancer Centers

Committee Management Officer **Grace Tato**, of the NCI Division of Extramural Activities

two things, first that merit scores are in fact linear, and the merit process by itself actually ranks merit in a linear way rather than in a non-linear way or a discrete way.

So at one end of the spectrum, low is low and it doesn't matter how lower than low you are, and then there's random noise, and at the upper end there's probably… so one question is there actually a linear relationship between measured merit and real merit.

The second is, for cancer center with 1x and a cancer center with 4x and both getting the same merit score, what happens to the size calculation in these models? Because I didn't see that addressed, when you have equally meritorious programs that are vastly different in size.

VARMUS: Let me address the first part of your question. As it turns out we're still working with the modeling, as Bill has indicated.

And one thing in that you're right, every site visit team may have a different impression of what a score of 12 means, and there are lots of factors that go into making up that score.

But it may well turn out that the modeling will work better using a percentile score, instead of an absolute impact factor score, and that's something we're still working on. But your question is right on.

SAWYERS: "I was captivated by one of the early conclusions, which was to reward the cancer centers for what they're good at and not penalize them for what they're not good at."

The other question we can answer by probably doing a little arithmetic. I can't answer that question off the top of my head, but maybe Linda [Weiss] can do it on the side and get you an answer to that, because there is a way to calculate that.

HAIT: The formula for size and complexity could probably take a working group in itself to get it to work just right. But Linda can give you some sense.

VARMUS: It goes without saying that some arbitrary decisions were made, you can't make these numbers perfect—the 15 percent the 30 percent—those are numbers that are compromises, and they're not going to be perfect for everybody. But the issue was not to create a perfect world, but make a better world.

HAIT: One of the interesting things that we looked at was the number of things that are supported by a center of a different size: the number of the shared resources, the number of senior leadership positions, etc., differ.

Generally speaking the size of the center, the larger the number of the shared services, etc. So that was one of the considerations.

JACKS: We have several people who want to chime in, I just want to note that Linda Weiss is here and she's taking all of this in. The comments are having an important impact.

CULLEN: First as somebody who feels a little bit responsible for having instigated this, I want to offer thanks to Harold for setting up the working group and to Bill and Linda for really doing a superb job of leading it.

I think, to the point that was just made, the thing that was most encouraging to me about the whole process was that there were a broad variety of centers represented, and people very quickly said: 'We have to make compromises here, and this is not a perfect formula and this is not a perfect recommendation.'

Clinical centers tend to bunch in a very narrow merit score range.

So I don't think the merit scores are a perfect representation of quality, but we gave that up, people acknowledge that. There are other parts of the formula that balance that. So I think it was very encouraging how many people quickly were willing to come up with compromises.

The question I have, and we talked about it a little bit in the working group—but I would be interested in responses from Bill or Linda or even Harold—that one of the major complexities that I see that's still unresolved is how this will be implemented.

This is a formula that ideally works if it is rebudgeted every year.

It's difficult to make five-year awards or phase this in over a gradual period of time and meet the intent of the revision.

HAIT: I can tell you from discussions that we've had, as you know, if you look at the extremes—you can do it all at once, as a change, as a mandate; you can phase it in slowly; or do something in the middle.

The working group didn't come to a final recommendation, we thought that would be up to the centers branch because not only is it complicated, but it's also sensitive, and also in our report it was pointed out that the way these changes are made my night be entirely under the control of the NCI.

There's another NIH group that takes a look at this. So we laid out the playing field, if you will. Harold, if you want to comment, that's where we left it.

VARMUS: We do have jurisdiction over how

it's phased in, but I don't think any of us have an answer to the question on what's the best way to do it. So I think Recommendation 2 weighs heavily here. [The group's Recommendation 2 is that center administrators be involved in planning for implementation of new approach.]

How do administrators talk to them about the impact of sudden versus gradual change?

We're open to suggestions. We're trying to do this as painlessly as possible so that productivity is not affected.

JUDY GARBER [director of the Center for Cancer Genetics and Prevention at Dana Farber Cancer Institute and professor of medicine at Harvard Medical School]**:** I can hardly imagine the complexity of your task, and I should just endorse what Bill Sellers said first, but I wonder if it would be possible to have more simulations?

We had one that showed that there will be huge adjustments in both directions for all cancer centers.

Roughly half of them will have an increase, but others will have huge declines. You can imagine that not all the cancer center directors will be pleased. The communities will have some challenge in adjusting to the message.

VARMUS: "It goes without saying that some arbitrary decisions were made, you can't make these numbers perfect—the 15 percent the 30 percent—those are numbers that are compromises, and they're not going to be perfect for everybody. But the issue was not to create a perfect world, but make a better world."

If your cancer center core grant goes down by more than 50 percent, what does that say about the merit of the work, and the support of the NCI for the research, which is after all the supposed message and the mission of the core grant support, and that's not to disproportionately penalize others.

I think you're going to have to come up with some very serious ways of displaying what you have achieved with this adjustment.

This certainly gets to more equity, if the goal is equity and having centers have closer amounts of rewards. But if the goal is supporting research, then you're going to have to have some way to display that that is not what is being penalized, and that you have a way to adjust for that.

I think if you don't, it's going to be very hard to justify all the work of the cancer center core grant applications—when the amount of money that you're really talking about is shrinking so dramatically—and finding a way to compare the measurement of merit when this is the case.

HAIT: That was clearly a very hot topic of discussion.

The perception that, if the funding model changed and you got less money, even if you did extremely well with your impact score, that there could be a perception in your community that you're not doing well.

Number two is that, as the grant gets smaller, especially for larger centers, does it reach a tipping point where it's no longer so valuable that the faculty doesn't glom onto it as they do now. I'm not sure glom onto is the scientific term, but you know what I mean.

OLUFUNMILAYO OLOPADE [Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, associate dean for global health, and director of the Center for Clinical Cancer Genetics at the University of Chicago Pritzker School of Medicine]**:** I really appreciate the thoughtfulness that went into the recommendations.

I was just wondering, without really focusing on the dollar amounts, whether it was possible to provide technical assistance or some other resources to centers that actually serve the purpose of the NCI, or they are in resource constraint situations.

So, if the mandate really was to distribute the efforts of the NCI through the extramural program—and because all politics is local, and people live in different geographic locations in this country—and if the effort is to try to get a cancer center within two hours for people who are in diverse settings, the question of equity is not only going to be reflected in the amount of dollars that you give to a center.

I'm just really concerned about those poor performing centers.

What are the additional things that the NCI can do as part of this review to think about more resources will be needed? We provide technical assistance to other countries, what kind of assistance could the NCI leverage to bring centers up.

Because I think, that at the end of the day, if we focus on the cancer patient and where they live, it's really not about the dollars, it's about what resources are transforming cancer research in their communities.

VARMUS: Well Linda you might want to tell me about what we do in response to a poor-

performing center.

We do provide that kind of technical assistance. It's a good point. And of course we are paying attention to distribution of centers and as you know the coasts are fairly dense with centers and the middle of the country—we're very happy to see a new center in Kansas—and that does pay a role.

WEISS: So the two-hour recommendation that was in the original legislation that started this program in 1971.

Clearly we have not exactly met that, and I think the reason is because there are very high standards to entering the program.

I want to start by saying that even though we do feel that we have an important role in representing the research needs of underserved populations, we also have very rigorous standards in terms of merit. You do not become an NCI-designated cancer center merely on the basis of the fact that your center is serving the underserved.

When a cancer center has difficulties in review, typically what we do is work with them.

We actually reduce the award fairly dramatically. We usually limit the number of years; it's a lesser number of years than the five-year award a center typically gets. And we work with them fairly closely through more frequent progress reports and meetings to try to see how they are addressing the deficiencies that were addressed in the review.

Sometimes these are fairly temporary problems that come about due to changes in leadership in the university setting, and in matrix centers this can have some implications. Sometimes they're longer term.

I think that the NCI designation is such a desirable designation, not just because of the money that comes with it, but because in and of itself it brings the ability to leverage so many other resources that in almost every case, centers will in fact make significant progress and in their next review come back to par.

That's not necessarily always the case.

Sometimes the changes are significant enough that we have to work a little longer and we continually assess that with Harold and other NCI leadership to see how we want to go forward with this center. What are the remaining issues? But there is a process and we do provide some assistance from a programmatic point of view.

JACKS: I think Funmi was also suggesting that beyond the poor performing centers, just the centers program as a whole, can benefit from the NCI in many different ways beyond the budget they get from the CCSG, which of course you know as well, and that can always be enhanced.

Bill, I had one question for you related to the tenure. Harold mentioned earlier the OIGs and the pushback about getting seven-year awards. One way to reduce the administrative burden is to lengthen the award. It is five years for probably historical reasons. Did that ever come up in discussion?

HAIT: I don't think that came up. But it would certainly decrease administrative burden.

WEISS: I could speak, maybe, briefly to that.

We did have a stipulation in the guidelines that those centers scoring in the outstanding range—this was under the old scoring system, so that was the top range—could in fact have a sixth-year extension.

GARBER: "If your cancer center core grant goes down by more than 50 percent, what does that say about the merit of the work, and the support of the NCI for the research, which is after all the supposed message and the mission of the core grant support, and that's not to disproportionately penalize others."

NIH policy and other factors I think caused us to cease that policy at least temporarily. We have not reinstituted it as yet. One of the other problems we had was that created real havoc with the receipt schedule, because we were sliding cancer centers from one receipt year to another, so it just became complicated.

VARMUS: Two other issues, Tyler:

One is having an opportunity every five years to readjust by being evaluated and perhaps doing better.

The other, which I've found as a cancer center director, is that the five year review was actually a time to focus on the center—is the center set up right?

I found that when I came to Sloan-Kettering, I wanted to change the way the place was organized, and the cancer center grant gave me the opportunity to do that. Everybody applauded the idea that we show ourselves in a different, reactivated light—that this was going to be good. And it really gave me a weapon to use against the conservative forces within the institution.

WEISS: One other comment, we certainly are willing to take forward the thought about further streamlining the grant application.

We've done some of that I think with the 2012 guidelines, we've eliminated a lot of the shared resource data collection that we've had.

I think that will be an ongoing process. I do however want to make a plug for ensuring that we maintain the rigor of review for these, because otherwise you ultimately do dilute the power of the designation.

VARMUS: There's no doubt that the rigor of the review can be maintained without as much paperwork that is required by the process, and we really need to work on that.

WEISS: There's no paperwork now, Harold it's all electronic.

VARMUS: Haha, fine.

JENNIFER PIETENPOL [director, Vanderbilt-Ingram Cancer Center, B.F. Byrd, Jr. Professor of Oncology at Vanderbilt University Medical Center]: I just want to thank Bill and Linda and the task force again for going through this because it isn't easy. Like you said, it's a very contentious topic.

I want to second what Bill has said, and what Judy alluded to, which was the overall budget.

When I look at slide five, and what the description of what the cancer center program is, there are powerful words in there. "Envy of the world." But it's about 3 percent of the budget—3.5, 5 percent?

About $160 million? But that probably needs, as Bill is saying, to be looked at again, and especially relative to Judy's comments.

VARMUS: I resonate with this, and I don't need to make the case again.

I think some of the question that the NCAB might want to think about and take up at the next meeting, is whether you want to endorse the idea of an increase, and whether an increase in the cancer center budget comes out of other budgets.

To make a significant change would be pretty expensive. I'm also acutely aware that other institutions of the NIH have centers, and some of them are a lot more costly than ours. I won't mention names, but everyone knows what some of them are. I think we get enormous bang for the buck.

But before saying these are the pride of the world—or the envy of the world, and the pride of the U.S.—and we need more money for them, it would be very useful to think about what the CCSG money goes to.

After all, there are many other ways in which we support cancer research at these institutions, not the least of which is grants and SPORES and P01s and everything else. I think it would be very useful to say what would happen if we were to increase the cancer center budget overall by 1 percent, 5 percent, 50 percent, 100 percent?

Does that make sense? It's hard for you to gauge what the likely impact is, because it would be up to us to decide if we went along with some recommendation from the NCAB about the overall center's budget. Where would reductions be taken? That's not an easy question these days.

PIETENPOL: I want to applaud Linda and the team for how they put the supplement method in, how the global health supplements have come in, and how some of the PDX supplements—because that's part of this renovation. It enables really rapid mobilization of workforce.

It's pivotal; you can pivot on various needs.

VARMUS: And the great thing about the supplements is that it doesn't go into the base.

I'm a huge of supporter of this and I think 5 percent is a lot of money. I'd also point out that we could use this mechanism not just for the NCI-designated cancer centers but also for other NCI-supported institutions that get money, for example for our NCORP [NCI Community Oncology Research Program] web of centers and clinical trials.

There are many minority populations that are adjacent to those centers, and we can make better use of those centers for some of the things that have come up here in the discussion.

JACKS: To bring this discussion to a close, and it was a good and healthy discussion, thanks again to Bill and thanks to his group, to Linda, to the NCAB for their participation today.

This is not a formal report as you heard so we will not be looking for approval or acceptance of the report. There will be a more formal report in the future, so we will be hearing about it again to accept and approve.

But this was a good discussion, and just to follow up on what Harold was finishing with, there seems to be a sentiment around the table that this issue of the size of the national cancer centers programs is worthy of consideration beyond what we just heard and it has implications for the budget as a whole. It relates to Bill Goodwin's [chairman and president of CCA Industries Inc.] subcommittee on the budget and strategy, he discussed it a bit last night.

So I think we probably will take that up in some form, and realize that it won't be the simple task of doubling its budget, because it does have these implications.

News Analysis

Myriad Continues to Fight As Judge Denies Injunction

(Continued from page 1)

On March 10, Judge Robert Shelby from the Federal District Court for Utah denied Myriad Genetics' motion for a preliminary injunction against its competitors that had entered the market starting June 13, 2013, when the Supreme Court handed down its ruling in *Association of Molecular Pathology v. Myriad Genetics.*

The key conclusion in Judge Shelby's ruling is that Myriad and its co-plaintiffs are "unable to establish that they are likely to succeed on the merits of their claims."

The case may now go to trial or get settled out of court. If it goes to trial there will be several more steps, including hearings to interpret the claims, a vigorous process of discovery to uncover facts and documents, and then a possible trial.

Just Shelby's ruling is 106 closely argued pages. It is dense and intricate, but clear. Basically, he concedes that Myriad will suffer irreparable harm, but does not have a persuasive case it will prevail on the merits. The main reason is that the claims to DNA molecules—mainly to DNA primers used to amplify the DNA in its tests—are in trouble; and the claims to methods are in very deep trouble.

BRCA1 and BRCA2 are the most commonly mutated genes associated with inherited risk of breast and ovarian cancers. They are also the most commonly tested genes in the human genome. BRCA genetic testing is the most lucrative application of diagnostic genomics to date, having generated over $2.8 billion in revenues for Myriad Genetics, of Salt Lake City, since 1996. Based largely on its patent estate, Myriad had an almost complete service monopoly for BRCA testing in the U.S. from 1996 until June 13, 2013, the day the Supreme Court handed down its ruling and competitors entered the market.

The court unanimously ruled that DNA molecules with sequences corresponding to those found in nature are not patent-eligible, but engineered DNA molecules not found in nature (such as complementary DNA or cDNA) can be patented, so long as the claimed invention meets the other patent criteria of utility, novelty, nonobviousness, enablement and written description.

Justice Clarence Thomas wrote the Court's unanimous opinion. It was clear that there is a line somewhere between genomic DNA (not patentable) and cDNA (patentable), but the court was largely silent about where that line is; and no one has a map locating this Rubicon.

While the decision culminated a four-year odyssey through the federal court system initiated by the American Civil Liberties Union, it did not end the story.

Litigation Since the Supreme Court Ruling

Even before the Supreme Court ruling, Myriad Genetics was reassuring stockholders that the case only challenged 15 claims in seven patents, whereas the company had rights to 24 patents and over 500 claims. Myriad made good on its threat to enforce some of those claims less than a month after the Supreme Court ruling. On July 9, 2013, Myriad and other plaintiffs sued Ambry Genetics, which had started offering BRCA testing on the day of the court decision. Myriad then sued Gene by Gene, a Texas testing laboratory, the following day. It has since sued GeneDx, InVitae, LabCorp, and Quest Diagnostics.

On February 7, 2014, Gene by Gene and Myriad announced an out of court settlement. Among them, the lawsuits are asserting claims in fourteen BRCA patents and four patents on MUTYH, to which Myriad also has exclusive rights for colorectal cancer testing.

In the Myriad-Gene by Gene settlement, Gene by Gene agreed not to offer BRCA testing in the United States until at least February 2016, except when BRCA1 and 2 are merely part of whole-genome assays. All but one of the remaining five cases have been consolidated in the court of Judge Shelby in the Utah federal district court, the same judge made famous by striking down Utah's statute against same-sex marriage. He attended a tutorial on the science, and held three days of hearings in September and October 2013 before handing down his ruling March 10, 2014.

Why would Myriad sue?

After all, it lost its five broadest method claims over BRCA1 and BRCA2 to a unanimous decision by a three-judge panel of the Court of Appeals for the Federal Circuit, and Myriad lost its claims on isolated genomic DNA in a unanimous Supreme Court decision.

Several reasons come to mind. First, Myriad earned over $520 million in revenues from its BRACAnalysis and BART tests in its most recent fiscal year—and in the post-Angelina Jolie surge, it has reported its two best quarters ever.

The $10 million that Myriad's executives announced setting aside for the patent litigation, initiated since the Supreme Court decision, constitute just a week's revenue from their flagship product. Moreover, the litigation imposes substantial costs

of entry to competitors even if they win—unless the victors eventually recover litigation costs (the rules for which are currently on appeal in two cases before the Supreme Court).

Each new lawsuit against a competitor carries low marginal costs on Myriad, but much higher costs of defending a suit away from the home court on the defendants. If the initial Ambry and Gene by Gene lawsuits staved off entry of new competitors by even a few weeks, the action more than paid off the costs of litigation.

Myriad may also believe it will prevail. The early betting on the previous suit was in Myriad's favor, and the current cases are closer to classic patent fights among competitors. In the previous case, the American Civil Liberties Union was mounting a public interest case against Myriad to change the law, with no expectation of financial reward. These post-Supreme Court suits are cases are about the money, and companies are the primary plaintiffs and defendants. It is now a classic fight among competitors. Gene by Gene's early retreat suggested maybe competitors would lose their challenges. Judge Shelby's ruling, however, sharply readjusts those odds against Myriad.

In addition to the six cases filed by Myriad, two firms (Quest and Counsyl) have sought declaratory judgments that they are not infringing any valid patent claims in federal district courts in California. Ambry (initially joined by Gene by Gene) also countersued, alleging violations of antitrust law and denying infringement of any valid patent claims.

InVitae is also fighting back, seeking declaratory judgement of noninfringement in a California federal district court, and also challenging Myriad's choice of venue in Utah, given that InVitae had deliberately excluded customers from Utah.

The pending cases involving Myriad against Ambry, Quest, Counsyl, and Quest have been consolidated in the Utah district court, under Judge Shelby. The Labcorp and Invitae suits are also pending, at this point separately.

Basically, Myriad launched a vigorous patent offensive after the Supreme Court ruling. Judge Shelby is now deciding whether to grant a preliminary injunction that would block competition while the case proceeds further.

This is a high stakes game, and litigation is how the game works. Either the courts will decide or the parties will settle to reduce the considerable uncertainty facing both sides.

Like the Denver Broncos' donnybrook in the Meadowlands, a strong offense might meet a strong defense. Patent litigation is highly unpredictable, true *a fortiori* in a case following so closely on the heels of a unanimous Supreme Court that was mainly adverse to Myriad's claims on DNA molecules. Now Myriad faces an adverse ruling on the patents' merits in district court, the very court that will hear the cases if this progresses further.

Several features did not come out in Shelby's ruling that are likely to become much more apparent if this case goes to trial. Shelby's analysis conceded that Myriad and Utah were the discoverers. That is open to question regarding BRCA2. His analysis focused predominantly on whether the patent claims were *eligible* to be patented, and did not advance to points on which several claims may be even more vulnerable. Most of factors that Judge Shelby did not delve into further weaken Myriad's case.

Does Myriad have rights to BRCA2?

The race to find mutations associated with inherited risk of breast cancer started with Mary-Claire King's announcement of linkage to chromosome 17 in fall 1990. As Kevin Davies documented in his book Breakthrough, it is widely accepted that the team led by Mark Skolnick of the University of Utah and Myriad Genetics won that race to find BRCA1. They cloned and sequenced the gene and identified the first high-risk variants several months ahead of King and other rival groups in the UK, France and the United States. Utah/Myriad filed the first patent applications on BRCA1.

It was clear at the time, however that some families harbored mutations in other genes. A U.K. group led by Michael Stratton, from the Cancer Research Campaign, published linkage to chromosome 13 in 1994, setting off a second race to find BRCA2. Myriad filed its first BRCA2 patent application on Dec. 18, 1995, just three days before the Stratton group published its BRCA2 discovery in Nature. The scientific scuttlebutt has long been that Myriad scientists learned of the pending publication and filed just in time. But was it really in time?

The Stratton group, working with Andrew Futreal of Duke, filed a U.K. patent application on BRCA2 on Nov. 23, 1995 (U.K. patent 2,307,477 was published on May 28, 1997). The Stratton team submitted their BRCA2 paper on Dec. 5. Stratton's U.K. patent application was thus filed almost a month before Myriad's U.S. application for BRCA2, and the Myriad/Utah team did not publish on BRCA2 until March 1996, three months after Stratton's team. The

Stratton team also got a U.S. patent (6,045,997). That patent was allowed to lapse when the first maintenance fee was due, but the U.S. patent and patents in 18 other jurisdictions do establish a presumption of priority from Stratton's U.K. patent.

The U.S. Patent and Trademark Office is not supposed to grant overlapping claims, and U.S. law is clear in granting rights only to the first inventor (until the rules changed to "first inventor to file" in 2011). USPTO nonetheless did grant patents with claims that on first blush appear to overlap extensively for both BRCA1 and BRCA2.

For reasons that cannot be discerned from the public record, USPTO did not declare an "interference"—the intricate administrative procedure conducted by USPTO's patent appeals and interferences board to sort out priority of invention—that is, who gets which patent rights. The current litigation could finally bring to light the documents that would establish who knew what when, both who made the discovery and who deserves any patent rights on which mutations and the wild type sequence of BRCA1 and BRCA2.

Utah and Myriad are the presumptive favorites for whatever patent rights the courts confer for gene discovery of BRCA1, but Stratton's U.K. group appears to have the best prima facie case for priority on BRCA2; Myriad could wind up with subordinate, weak, or no BRCA2 rights at all. This should have been settled eighteen years ago, but perhaps it will finally be addressed through the discovery process if current cases proceed further.

Are the primer claims enabled and adequately described?

Most of the claims being asserted against Myriad's competitors center on amplification of isolated DNA. The Supreme Court ruling explicitly acknowledged that claims on man-made molecules—such as primers or probes or cDNAs—would be patent eligible, but only so long as they also fulfill the other patent criteria. The question is: do the claims on primers pass the tests for validity?

On March 4, the USPTO issued new guidance for granting patents after the *Mayo* (2012) and *Myriad* (2013) decisions of the Supreme Court. By the USPTO criteria, claims on pairs of primers and PCR amplification might cross the threshold to be eligible to be patented, since while the sequences themselves are naturally occurring sequences, the claims are not just to such molecules.

Claim 20 of Myriad's patent 5,747,282 claims *pairs* of primers for PCR amplification and subsequent sequencing. Those primers were specifically selected to amplify a particular segment of DNA, and thus require human ingenuity. Moreover, there are other ways to study or make the DNA and the underlying genes without making those particular molecules, so they do not pre-empt all uses.

But Judge Shelby's analysis, arguably different from the USPTO guidance, is quite clear that the primers are likely to be deemed ineligible to patent because they are useful only to the degree their sequences match naturally occurring sequences, and he explicitly rejected the "pairs" sufficing to confer patent eligibility. Even if these claims survive as patentable subject matter, however, they may come a cropper on other criteria.

PCR primer claims could fall afoul of enablement and written description. Myriad's BRACAnalysis test involves amplifying over eighty DNA segments ("amplicons") from BRCA1 and BRCA2, sequencing the individual amplicons, and then stitching together the sequence of both genes in a computer. The actual sequences for most primer DNA molecules, however, lie outside of cDNA sequences. PCR primers to get all the DNA for an exon have to be situated beyond the exon. They flank it. The primer sequences thus do not appear in the cDNA sequence that was disclosed (with some errors) and specified in claim 2 of the crucial '282 patent.

A judge will have to decide whether claims to the primers are adequately described and fully enabled. Unless the actual primers and primer pairs are specified in the various documents submitted to the patent office, however, this could be trouble for Myriad's case. The criterion for enablement is that a "Person Having Ordinary Skill In The Art" (PHOSITA) could make and use the invention "without undue experimentation." For DNA sequences, a full written description is often taken to mean specifying the actual sequences, to demonstrate the patent-holder had them in possession when the patent application was filed. Case law can be found to support many different degrees of specificity, however. At one end of the spectrum, the court could decide it is sufficient to claim as broadly as "we found the gene so we can claim any primers that allow you to sequence it," or more narrowly, requiring the actual primer sequences to be specified.

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Is the claim to any DNA with a 15-bp stretch of BRCA1 sequence invalid?

Claim 6 of the '282 (DNA molecule) patent is one of the few claims that Myriad is asserting in the patents-in-suit that does not involve DNA amplification. It is also the only claim from the current suits that was challenged in the *Myriad* case that went to the Supreme Court. It claims any isolated DNA molecule, of any length, that includes a 15-bp stretch of the BRCA1 cDNA sequence.

This claim is probably invalid, and it may prove unwise to have asserted it, particularly because it clearly captures so many "genomic" DNA molecules that the Supreme Court ruled unpatentable. The examiner scored this claim as "subordinate" to the cDNA sequence claim 2, meaning it should be narrower, but its plain language meaning is vastly broader than the cDNA claim, and could be infringed by anyone creating any of millions of molecules.

This claim is chemically subordinate, in that it claims smaller molecules, but it is vastly more expansive in informational terms, and thus biologically broad, capturing an infinite class of molecules described by the claim language.

Molecules identical to 15-bp segments of BRCA1 sequence occur throughout the genome. Anyone who ever studied or did a diagnostic test for any DNA molecule that encodes five amino acids in the same order as any five-amino-acid sequence in the BRCA1 protein would infringe this claim, and many of those genes would not be from BRCA genes. The claim is thus vulnerable on grounds of novelty and obviousness.

This flaw was pointed out by Kepler and colleagues in 2010 (in Genomics) and refined in Kepler's 2013 testimony to the USPTO as well as independently reported by Rosenfeld and Mason in 2013 (in Genome Medicine). The patent's own definitions are vague, and are unlikely to rescue this claim. The only way to rescue this claim is if courts interpret it far more narrowly than its plain English meaning.

Will NIH's rights complicate Myriad's case?

The University of Utah had NCI grants at the time BRCA1 and BRCA2 were discovered. The resulting inventions thus appear to be subject to terms of the Bayh-Dole Act of 1980.

The University of Utah reported the BRCA1 and BRCA2 publications under these grants. Five of the BRCA patents appear to stem from this work. Two of the BRCA1 patents were reported to NIH and appear in the RePORT database. The other three BRCA1/2 patents that seem to arise from NCI grants were either not reported to NIH or are missing through clerical errors. (RePORT is a public database; iEdison is actually the main database to which institutions report inventions, but it is not available for public search.)

In addition to the University of Utah grants, Myriad/Utah's BRCA2 patents entailed collaborations with Endorecherche, University of Toronto, and University of Pennsylvania. Among these, Barbara Weber of UPenn also had NIH grants, and the UPenn license to Myriad (available through the SEC's Edgar database) explicitly acknowledges government Bayh-Dole rights. So even if Utah did not deem those particular BRCA2 patents covered by Bayh-Dole, UPenn clearly did.

Myriad/Utah's two core BRCA1 patents (5,710,001 on methods for detecting sequence alterations from wild type and 5,747,282 on DNA molecules) were initially filed without listing Roger Wiseman and Andrew Futreal of the National Institute of Environmental Health Sciences. NIH's Office of Technology Licensing contacted Myriad after the patent application was filed, and Wiseman and Futreal were added as coinventors. NIH then exclusively licensed its rights to Utah (thence licensed to Myriad). This means that the BRCA1 patents that were originally assigned to Utah and Myriad are not only subject to Bayh-Dole, but also the Stevenson-Wydler Act, which applies to inventions from federal laboratories, including the NIH intramural research program through which Wiseman and Futreal helped discover BRCA1.

The regulations implementing Bayh-Dole stipulate that government use rights should be acknowledged in the patent. This does not appear to have been done for any of the five BRCA1 and BRCA2 Myriad/Utah's patents subject to Bayh-Dole or the two patents that are also subject to Stevenson-Wydler.

A further wrinkle is the absence of NIH from the list of plaintiffs. The licenses from UPenn, University of Toronto and Endorecherche (available through the SEC Edgar database) obligate those institutions to support litigation raised by the exclusive licensee—the University of Utah, which in turn conveyed exclusive rights to Myriad. The NIH, however, presciently included a "no ligitation for 90 days" clause and other escape provisions in its license. Since the lawsuits against Ambry and Gene by Gene were filed just three weeks after the Supreme Court ruling (the firms announced they were offering BRCA testing the day the decision was handed down), this clause in NIH's license was not honored. That may be one explanation for why NIH did not join the suit; it was not obligated to, given the violation of terms in its license.

It is telling, nonetheless, that NIH opted not

to join the plaintiffs. It surely could have chosen to do so. The lawyers opposing Myriad will likely want to explore NIH's views on Myriad's use of the patents, and why NIH did not sign onto the suit. The failure to acknowledge government use rights in the patents, combined with NIH's absence from the suit will complicate Myriad's arguments if this is deemed material to the case.

Andrew Futreal, in particular, could become a pivotal figure in understanding the discovery process in court proceedings. He was a coauthor and co-inventor on the Myriad/Utah team that first characterized BRCA1 when he was at NIEHS, and then coauthor and coinventor on the Stratton papers and patents that first reported BRCA2. By then, he was a faculty member at Duke. He is thus the only person who was coauthor and coinventor for the first papers and patents for both BRCA1 and BRCA2.

Will Myriad's arguments from 1997 undermine its arguments in 2014?

If the story were not already sufficiently convoluted, there is yet a further twist.

Several of the patents now being asserted by Myriad were originally assigned to OncorMed and Gene Logic. Myriad filed lawsuits against OncorMed and the University of Pennsylvania in December 1997, soon after Myriad was granted its first BRCA1 patent (5,693,473). OncorMed had gotten a patent that August (5,654,155).

OncorMed fired the first volley, filing suit against Myriad before Myriad was granted its first BRCA1 patent. Despite getting a patent earlier, however, OncorMed was in a weak position because it had actually filed its application later than Utah/Myriad (August 1994 for Utah/Myriad/NIEHS; February 1996 for OncorMed). The examination process was considerably faster for OncorMed's first BRCA1 patent, but if the patents went into interference or litigation, OncorMed had the weaker hand based on presumptive priority. OncorMed settled out of court, agreeing to exit the BRCA testing market and conveying its patents to Myriad, which later got them formally reassigned. Those patents are now among the patents being asserted against Myriad's current competitors.

That puts Myriad in the position of asserting patents in 2014 that it was arguing against in 1997. The UPenn suit was filed but never served, as UPenn quickly agreed to cease commercial BRCA testing. The OncorMed suits, however, went to court before reaching settlement. The 1997 litigation may have have left a paper trail that the discovery process will unearth. Myriad could find itself confronting its own arguments against these patents from seventeen years ago. This is not unprecedented, but nonetheless a potential complication. Claims in the OncorMed patents were likely to be revoked or considerably weakened in 1997, and they are no more likely to be robust and enforceable now.

Stay tuned

Litigation is unpredictable. Most cases that go to court do so because each side is confident enough of prevailing to incur the litigation costs.

The parties could settle out of court. This is what has happens in the vast majority of cases. Some of the laboratories that have been sued may have entered the market precisely to ensure that they would be part of any oligopoly that might emerge from a settlement—which could shut out future competitors not party to the litigation.

The importance of the data needed to interpret the clinical significance of rare variants is another distinctive feature of these cases.

Myriad's choice in 2004 to stop sharing data and cultivate a proprietary database as a trade secret is raised in pleadings from both sides. That is a matter for a separate analysis, however, and bears on other areas of law beyond what can be patented and whether valid claims are infringed, the core issue in these cases.

It is worth noting, however, that the judge did have some tart words for Myriad in his penultimate paragraph. In commenting on Myriad's choice to hoard its mutation data as a trade secret, Judge Shelby observed: "Myriad has chosen a commercial path that turns much of our patent policy on its head."

The historian in me wants this to go to court so we can learn what happened two decades ago. Litigation is very costly, however, and the trial and appeals process is protracted, saps management attention, and poses recurrent decisions about whether and how to proceed further.

Moreover, litigation is a very expensive and not entirely reliable way to document historical events.

No one predicted a safety on the first play from scrimmage in the Super Bowl; and any number of outcomes can still emerge from the litigation over BRCA1 and BRCA2.

The business models that emerge, however, are likely to entail more competition than Myriad's unitary genetic testing service that prevailed for 17 years, from 1996 to 2013.

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