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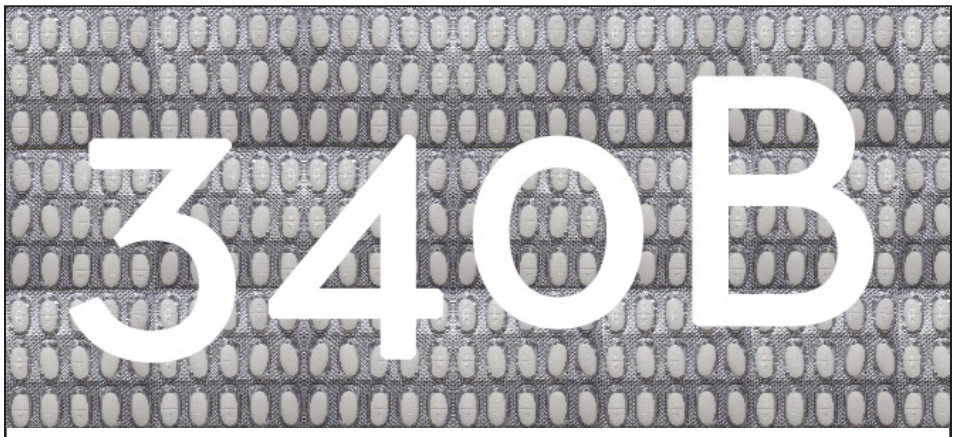

Judge's Order Likely to Derail Federal Rule Clarifying 340B Drug Discount Program

By Paul Goldberg

Many people love the 340B Drug Pricing Program.

Hospitals, clinics and cancer centers rely on it to buy drugs at discounts as deep as 50 percent—and then collect reimbursements that don't reflect the discount.

Many others hate 340B, arguing that the federal program gives qualified providers an unfair advantage, and making it even more difficult for office-based oncology practices to survive.

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Guest Editorial

Accelerating the Pace of Scientific Progress

By Brian Druker

We are facing a disturbing paradox in science. We have unprecedented potential for advancements spurred by current technologies. But at the same time we are confronting flat to declining funding.

This climate provides a unique opportunity to examine and improve how we fund research.

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In Brief

Kraft Named Director and Associate V.P. Of University of Arizona Cancer Center

ANDREW KRAFT was named director of the **University of Arizona Cancer Center** and associate vice president for oncology programs for the University of Arizona Health Sciences Center.

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ACA Extended 340B Program To Free-Standing Cancer Centers

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According to critics, the program is poorly defined, and is increasingly abused by entities that don't need help from the government.

Discounts don't necessarily reduce aggregate costs of medical care, critics say. Pharmaceutical companies can make up for lost revenues simply by increasing the prices.

Established in 1992 to benefit hospitals and clinics that serve the needy, 340B has expanded exponentially in recent years. About a third of the country's non-federal hospitals qualify for the program, and 340B now accounts for about 2 percent of the $325 billion U.S. retail spending on prescription drugs.

Over the past several years, many key players in oncology have been questioning the program's expansion and its eligibility criteria. All of these disparate interests—those who love 340B and those who hate it—have been waiting for the federal Health Resources and Services Administration to issue a "mega-rule," which is expected to define who should qualify for 340B discounts.

Insiders say that the draft mega-rule has been completed by the agency and is undergoing review by the Office of Management and Budget.

Its eagerly anticipated release, expected to occur later this June, appears to have been pushed off into the future, thanks to a recent ruling by a judge at the US District Court for the District of Columbia.

Federal Judge Rudolph Contreras challenged HRSA's authority to make a legislative rule on the 340B program, invalidating the agency's attempt to expand the discount program to include uses of orphan drugs.

By finding that the agency lacks authority to make a legislative rule on orphan drugs, the Contreras decision raises questions about HRSA's ability to promulgate legislative rules for the 340B program as a whole.

The Contreras May 23 decision on orphan drugs leaves little to imagination:

"The rulemaking authority granted HHS by Congress under the 340B program has…been specifically limited, and HHS has not been granted broad rulemaking authority to carry out all the provisions of the 340B program. Instead, Congress has limited HHS's rulemaking authority to creating a system for resolving disputes between covered entities and manufacturers—not to engaging in prophylactic non-adjudicatory rulemaking regarding the 340B program altogether.

"While the Court agrees that a prophylactic rule like this seems like the most reasonable way for implementing the orphan drug exclusion, unfortunately, Congress did not delegate to HHS broad rulemaking authority as a means of doing so."

In a nutshell: the federal agency that oversees the 340B program lacks authority to regulate the program's scope and include the rules in the Code of Federal Regulations. The agency could—perhaps—issue an interpretive rule.

"HRSA is assessing the impact of the ruling on the proposed 340B omnibus rule," David Bowman, a spokesman for the agency, said in an email to The Cancer Letter. "HRSA will convey information as soon as we know a path forward."

Many drug makers view 340B as a way for the government to extract substantial discounts for a growing number of patients and healthcare providers. Though the Pharmaceutical Research Manufacturers Association supports a limited 340B, the industry group last year challenged the program's expansion to cover some uses of orphan drugs, ultimately triggering the ruling by Contreras.

Contreras was appointed to the bench by the Obama administration.

Organizations that represent office-based oncologists see the 340B program as way for their competitors—non-profit hospitals—to get deep discounts on drugs. Operators of oncology practices argue that as hospitals grow stronger, they swallow independent outpatient clinics, which are unable to get drugs at such low prices.

Proponents of the 340B program say that it makes

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it possible for rural and inner city hospitals to stay open. Private practices often cherry-pick patients, sending those who can't pay to safety net hospitals, advocates contend. Finally, according to the program's supporters, practices are going out of business or selling out for a variety of reasons, many of them unrelated to 340B.

Under the Affordable Care Act, eligibility for 340B was extended to freestanding cancer hospitals that are excluded from the Prospective Payment System.

Three of these newly eligible hospitals have completed the certification.

City of Hope National Medical Center obtained eligibility for its main campus in 2010, University of Miami Sylvester Cancer Center and its clinics have been in the program since 2011, and the University of Southern California Norris Cancer Hospital and its clinics joined the program in 2014, HRSA documents show.

Insiders say that many freestanding cancer centers are unable to meet the eligibility requirements for 340B because they don't treat a sufficient number of low-income patients.

Others may be able to get substantial price through group purchasing organizations or other arrangements with manufacturers.

What if there is no Mega-Rule?

The mega-rule, which now appears to have stalled, was expected to clarify some very important controversies about 340B:

• *Defining Covered Entities:* the number of entities has been on the rise from the start. According to a 1994 rule, outpatient facilities that are bill Medicare as integral components of hospitals qualified for 340B. In 2003, Congress opened the door to include more rural hospitals and small urban hospitals. In 2005, some children's hospitals were allowed to join. And in 2010, the Affordable Care Act included the outpatient settings of free-standing cancer hospitals, rural referral centers, sole community hospitals, and critical access hospitals.

• *Defining Patients:* Under HRSA's 1996 definition, patients qualify for 340B discounts if: (1) the covered entity has established a relationship with the individual, such that the covered entity maintains records of the individuals health care; and (2) the individual receives health care services from a professional which is either employed by the covered entity or provides health care under contractual or other arrangement (e.g. referral for consultation) such that responsibility for the care provided remains with the covered entity; and (3) the individual receives a health care service from the covered entity which is consistent with the services for which the grant funding or federally qualifies health care center look-alike status has been provided to the entity. In 2011, the Government Accountability Office noted in a study that HRSA's definition of patient raised concerns that the guidance may be interpreted in ways that are inconsistent with its intent.

• *Defining Contract Pharmacies:* In 1996, HRSA extended to entities that did not have an in-house pharmacy to contract with a single outside pharmacy. In April 2010, the agency allowed contracts with multiple pharmacies. According to the agency, over 14,000 pharmacies now dispense 340B drugs.

"This is a program that is in real need of rulemaking and, potentially, of reform, and the judge's ruling has put the rulemaking in jeopardy," said Jeffrey Ward, an oncologist at Swedish Cancer Institute who served as chair of the American Society of Clinical Oncology Clinical Practice Committee at the time when it developed a policy statement on the 340B program.

"I think the two things that HRSA can do is require transparency and to define the patients," said Ward, who is the current chair of ASCO's Payment Reform Workgroup. "That may in and of itself be sufficient, but if they can't do that, then Congress will eventually act, and it won't be to the benefit of the program or the hospitals in the program."

Maureen Testoni, general counsel of Safety Net Hospitals for Pharmaceutical Access, a Washington coalition, said that the outcome of the controversy would be shaped by whether the Department of Justice would appeal the Contreras ruling on orphan drugs.

True, the ruling questions the HRSA authority to make a legislative rule, but it doesn't preclude the agency from making an interpretive rule that would clarify the existing guidances.

"The idea behind the mega-rule was that they were going to take a lot of the guidances that they have put out in the past and they were going to publish those in a formal regulation that would be in the CFR," Testoni said to The Cancer Letter.

"As part of that, they would be clarifying some of the guidances that were issued years ago. If you don't put it in the Code of Federal Regulations, you still have that guidance. It's still out there, it's still valid, people are still using it. Our association has said that we would like to see some clarification of certain aspects of different guidances. They can still make clarifications. It doesn't have to be done in a legislative rule."

In the absence of clearly defined rules governing 340B, oncology will remain the "Wild Wild West," said Barry Brooks, a Dallas oncologist who serves as chair of the Pharmacy & Therapeutics Executive Committee at US Oncology Network. "Where are we? It's where we've been, which is no rules. Community oncology can't continue with the advantages that are afforded to the 340B hospitals. And not 340B hospitals still get site of service 100 percent more for all of the same things we do in the clinic. We are bleeding to death slowly. US Oncology will bleed to death last, because we are the most efficient organization, but unless we get some sort of legislative relief or bureaucratic interpretations that help us, we are not in a very good place."

Ted Okon, executive director of Community Oncology Alliance, said that the current uncertainly may require Congressional action.

"If there is no rule, then it is going to be up to Congress to do one of two things: either give HRSA authority through legislation to be able to do rulemaking or it would be totally up to Congress to legislate what HRSA wanted to do, and possibly even more," Okon said to The Cancer Letter.

Rena Conti, assistant professor of health policy and economics at the University of Chicago, said the 340B discounts don't lower the price of drugs.

"I have two problems with the program as currently implemented," Conti said. "First, many discounts don't get passed on to patients. Second, the increasing availability of the discounts pushes up the prices of cancer drugs for us all."

The Orphan Drug Imbroglio

The controversy over HRSA's authority emerged late last year, when the agency published a legislative rule that sought to provide coverage for some uses of orphan drugs.

Under the Affordable Care Act, the indications covered by the orphan drug designation are exempt from discounts under 340B. Thus, for diseases that affect fewer than 200,000 people in the U.S. and that have been recognized as orphan indications by FDA, there would be no discounts.

The logic was straightforward: pharma companies need to be incentivized to develop drugs for smaller populations. At FDA, these drugs are exempted from the application user fee, and when approved, they receive longer exclusivity.

However, orphan drugs are often used in ways not covered by the orphan designation, and here, HRSA put together a final rule that would have mandated 340B discounts for these off-designation uses at entities that were allowed to join the program under ACA.

The amounts of money involved could be substantial. Consider Prozac (fluoxetine): the drug has orphan designations for the treatment of autism and body dysmorphic disorder in children and adolescents. However, Prozac is mostly prescribed for depression, not its orphan designations. Under HRSA's published rule, Prozac prescribed for depression would have been subject to 340B discounts.

Similarly, the drug Rituxan (rituximab) would have been exempt from 340B discounts when used within its orphan designations—anti-neutrophil cytoplasmic antibody-associated vasculitis, non-Hodgkin's B-cell lymphoma, and immune thrombocytopenic purpura. However, Rituxan would have been subjected to discounts when prescribed for the non-orphan conditions of rheumatoid arthritis, multiple sclerosis, and autoimmune anemia.

In addition to being resistant to offering these discounts, drug companies complained that the rule created unreasonable reporting requirements. Pharmacies couldn't be expected to know whether the Rituxan they are dispensing is being used within its orphan designation oroutside it, they said.

PhRMA sought an injunction, claiming that the HRSA rule was "based on an erroneous reading of the statutory text that HRSA is seeking to implement and is outside the scope of HHS's rulemaking power."

The PhRMA complaint, filed on Sept. 27, 2013, contends that HRSA took liberties with the language of the ACA.

The statute reads that 340B discounts will not be given on drugs "designated by the Secretary under section 526 of the Federal Food, Drug, and Cosmetic Act for a rare disease or condition."

However, the language of the HRSA regulation rephrases that exclusion to read that 340B discounts would not be given for drugs "designated by the Secretary under section 526 of the Federal Food, Drug, and Cosmetic Act *and used to treat* a rare disease or condition."

With this seemingly microscopic revision, non-orphan uses of orphan drugs could be subjected to 340B discounts.

"HHS's revision of the orphan drug exclusion through rulemaking is at odds with the plain statutory text," the PhRMA filing states. "Moreover, HHS lacked authority to issue the Final Rule. Congress did not empower HHS or HRSA to promulgate rules interpreting the orphan drug exclusion. No federal statute—including the 340B statute as amended by the Affordable Care Act—comes even remotely close to authorizing the agency to issue rules related to Section 340B(e). HHS thus acted *ultra vires* [beyond its power] in promulgating the Final Rule, in further violation of the Administrative Procedure Act…

"If Congress had intended to impose this use-based limitation on the orphan drug exclusion, it could easily have done so."

In his decision, Contreras concurred with PhRMA's argument, concluding that HHS lacked "the statutory authority to engage in such rulemaking." His ruling vacated the HRSA final rule and granted the plaintiff's motion for an injunction and motion for summary judgment.

HRSA had exceeded its authority in reinterpreting congressional intent and edging into legal terrain covered by the Food Drugs and Cosmetics Act, the judge wrote.

"Though the Health Resources and Services Administration is considered a component of the U.S. Public Health Service, the rulemaking authority clearly applies to administrative issues such as regulations regarding uniforms, record-keeping, etc.—not implementation of any and all statutes related to the public health," he wrote.

"The procedures for implementation… clearly refer to the process for orphan drug designation in the first instance—which is handled by the FDA—not HRSA under the 340B Program. Importantly, Title 21 of the United States Code pertains to the FFDCA; the 340B Program, meanwhile is part of Title 42 and the PHSA—an entirely different statute.

"A limited grant of rulemaking authority in an entirely different statute, therefore, cannot carry the day for the rulemaking here."

Contreras said he would be willing to consider an argument that the HRSA rule is interpretive, as opposed to legislative, perhaps upholding some of its parts while vacating others.

The U.S. Department of Justice didn't take him up on this offer. On June 12, a DOJ lawyers wrote to the judge that HHS is "evaluating its options as to how to respond to the Court's decision, including whether to appeal and/or whether to propound an interpretive rule or other type of interpretive guidance.

"HHS does not interpret the Court's decision as precluding it from issuing an interpretive rule or other type of interpretive guidance, even if that rule or guidance sets forth the same interpretation previously embodied in the challenged regulation."

PhRMA's executive vice president and general counsel, Mit Spears, said the Contreras decision places limits on HRSA's authority.

"We are extremely pleased with the court's decision," he said in a statement. "PhRMA strongly supports the 340B program, which was intended to help vulnerable, uninsured patients access life-saving medicines. We are committed to working with all stakeholders to improve the program. To achieve this important objective, it is critical that the program operates in a manner consistent with the clear and unambiguous direction of Congress."

The Safety Net Hospitals for Pharmaceutical Access said it continues to support 340B discounts in this setting.

"We strongly support the implementation of the orphan drug exclusion included in HRSA's final regulation," the coalition said. "The regulation allowed rural and cancer hospitals to access 340B discounted pricing on orphan drugs when used for common indications. Without access to these discounts, many hospitals will be forced to discontinue vital services for their patients.

"As the government explores its options, we strongly encourage HRSA to maintain its current orphan drug policy so rural and cancer hospitals are not faced with significant drug price increases and these safety-net providers may continue their missions to serve our nation's most vulnerable patients."

PhRMA's complaint, the judge's ruling, and the DOJ's response are posted on The Cancer Letter website.

Groups Organize Capitol Hill Push for Lung Cancer Screening

By Tessa Vellek

The Centers for Medicare and Medicaid Services have another six months to decide whether to cover low-dose computed tomography screening. Yet, proponents of screening seem unwilling to take the chance that Medicare coverage would be restrictive.

To tilt the scale in their favor, they have launched two congressional sign-on letters to CMS.

Spearheaded by Sens. Dianne Feinstein (D-Calif.) and Johnny Isakson (R-Ga.), the Senate letter has amassed 45 signatories. The House letter, authored by Reps. Charles Boustany Jr. (R-La.), John Barrow (D-Ga.), Jim Renacci (R-Ohio), and Richard E. Neal (D-Mass.), received 134 signatories.

"Providing patients at high risk of developing lung cancer with annual low-dose CT scans has enabled radiologists and thoracic surgeons to accurately diagnose and treat early stage lung cancer and, subsequently, save more lives," reads the House letter.

Both letters urge CMS to issue a final decision before the Feb. 25, 2015, deadline.

"We are writing to urge that the Medicare National Coverage Determination for low-dose computed tomography scans for Medicare beneficiaries with a high risk of developing lung cancer can be completely expeditiously," reads the Senate letter. "With the median age of lung cancer diagnosis being age 70, it is essential that seniors on Medicare have access to this screening tool."

This political action is orchestrated by the Lung Cancer Alliance and professional groups that would be expected to perform the screening. These include the American College of Radiology and the Society of Thoracic Surgeons.

LCA has been a longtime supporter of lung cancer screening, originally campaigning against the NCI-funded National Lung Screening Trial, which ultimately provided the basis for considering coverage of screening. In attacking the NLST years ago, LCA president and CEO Laurie Fenton-Ambrose described it as a failed and outdated trial. But in April, Fenton-Ambrose said she considers the trial "indisputable," and she is requesting Medicare coverage of the lung cancer screening based on the trial's results. (The Cancer Letter, April 18).

Proponents of CT screening for lung cancer have reasons to be concerned.

At a hearing April 30, the Medicare Evidence Development & Coverage Advisory Committee expressed low confidence in low-dose CT as a method for screening for lung cancer in the Medicare population.

Panel members gave low average confidence scores, on a scale from 1 to 5, in response to two questions focusing on harms: 2.22 for whether there is adequate evidence for significant benefit over harm, and 2.33 for whether harm will be minimized in the Medicare population. (The Cancer Letter, May 9).

Several committee members said they were skeptical of the generalizability and implementation of the positive NLST finding and U.S. Preventive Services Task Force recommendation. Members said it would be difficult to identify patients as high-risk for lung cancer, given the current ACR accreditation process.

"I got stuck on 'adequate,' and I just didn't feel that there is really adequate evidence at this time," said MEDCAC member Jo Carol Hiatt, chair of the Inter-Regional New Technology Committee at Kaiser Permanente. "It's promising, but we certainly need more information before making a broad statement about benefit to the Medicare population."

ACR called the MEDCAC vote a "failure" that may "place many seniors at risk." (The Cancer Letter, May 9).

Ultimately, Medicare's decision will show how a positive prevention trial translates into coverage.

NCI's National Lung Screening Trial, with 53,454 participants, found that low-dose CT screening had a 20 percent relative reduction in mortality. All participants were 55 to 74 years old and at high risk for lung cancer; they smoked over 30 packs per year and either stopped smoking less than 15 years ago or continued to smoke.

The U.S. Preventive Services Task Force gave a B rating to the procedure last fall, recommending screening for people between the ages of 55 and 80 who have a 30-pack-year history of smoking (The Cancer Letter, March 21).

The Affordable Care Act requires private insurers to begin covering recommendations with a B rating or higher, starting Jan. 1, 2015. However, Medicare is not required to follow the USPSTF recommendations.

There are three approaches for Medicare coverage on the table:

The first would only cover the screening for patients who match the NLST population.

The second—"coverage with evidence development"—would allow Medicare to continue to define risk groups, while limiting low-dose CT screening to only approved clinics.

The third—proposed by LCA and professional

groups—would offer full coverage to those meeting NLST requirements as well as provide coverage with evidence development to broaden those eligible for coverage.

These groups include: the Lung Cancer Alliance, National Comprehensive Cancer Network, American College of Radiology, the Society of Thoracic Surgeons, the American Association of Physicists in Medicine, the Academy of Radiology Research, American Association for Thoracic Surgery, the American Board of Radiology, the American Board of Radiology Foundation, American College of Surgeons' Commission on Cancer, American Roentgen Ray Society, American Society for Radiation Oncology, Association of University Radiologists, I-ELCAP, Prevent Cancer Foundation, Quantitative Imaging Biomarkers Alliance, Radiological Society of North America, Society of Chairs of Academic Radiology Departments, Society of Computed Body Tomography and Magnetic Resonance, and Society of Thoracic Radiology.

"The medical and patient groups want CMS to provide full national coverage for high-risk patients as defined in the USPSTF recommendations and provide coverage with evidence for other high-risk patients not included in USPSTF recommendations using data collected through existing registries," the coalition of 40 groups said in a joint press release March 13.

The expansion of coverage to "other high-risk patients" would include younger patients perhaps smoking less than 30 packs-per-year that have an additional risk factor as well as 55-80 year-olds who may have stopped smoking more than 15 years ago.

One major medical society, the American Academy of Family Physicians, an organization with 110,600 members, issued a clinical recommendation that opposes screening earlier this spring.

The screening recommendation released by ASCO would provide annual screening coverage for smokers and former smokers between the ages of 55 to 74 who smoked 30-pack years or more patients, as defined in NLST. Anyone not meeting these requirements would not be eligible for Medicare coverage.

Barnett Kramer, director of the NCI Division of Cancer Prevention, said to The Cancer Letter that it would be sensible to evaluate effectiveness of a screening modality after its efficacy has been determines. He said he supported the coverage with evidence development approach (The Cancer Letter, March 21).

Otis Brawley, chief medical and scientific officer of the American Cancer Society, said the difference between efficacy and effectiveness in lung cancer screening can be significant.

"Said simply, when introduced into the real world, low quality screening can be very harmful and even high quality screening of those at lower risk may have an unfavorable benefit to risk ratio," Brawley to The Cancer Letter March 21. "It can be net harmful."

In a related development, the American Medical Association House of Delegates voted June 11 to "recommend that coverage of screening low-dose CT scans for patients at high risk for lung cancer by Medicare, Medicaid, and private insurance be a required covered benefit."

The House and Senate sign-on letters are available online.

Guest Editorial

Druker: Proposals Should Focus On Impact, not Innovation

(Continued from page 1)

In this article, I will offer some personal perspectives on the current state of biomedical research, peer review, and our own efforts to implement change.

We are challenged by the continued stagnation of funding for biomedical research. Although we may recognize this as likely, we should not stop advocating for continued or even increased funding of research. Our arguments are strong. From an economic point of view, we know the return on investment in biomedical research is high. We can also emphasize that careers in scientific research are exactly the kind of jobs we want in the U.S. The third and most effective argument is that our research impacts human lives. But if we make this argument, we must be prepared to deliver on our promises as we will be held to them. This means setting goals and focusing on outcomes. To be successful at obtaining additional funding, our goals must be aspirational, but at the same time achievable and realistic.

If we contend that our research improves health, this by definition means we have to support translational research. This doesn't mean we can't and shouldn't fund basic research. As someone whose work was critically dependent on a solid foundation of basic research and as someone who has consistently said that the best translation comes from the best basic science, I fully support continued funding of basic research. The issue is trying to find the right balance between true exploratory basic science and basic science that supports translational research. There are many translational research questions that would substantially benefit from additional basic studies and these would easily be identified by thinking strategically about how best to accomplish our goals. What are we trying to achieve; what is the best way to achieve our goal; and how do we organize ourselves to achieve the goal?

As publicly-funded scientists, we also must strive to effectively communicate our work and its importance to the public. To do this successfully, we have to improve our abilities to speak in a manner that is interesting and approachable by the public. This means we have to learn or be willing to be taught how to communicate by using analogies and telling stories, without resorting to scientific jargon. We also have to think about more effective means of lobbying. As scientists, we should care about funding for all disciplines, not just cancer. This means working with all professional organizations to create a consistent and coordinated message. During sequestration, Senator Ron Wyden from Oregon asked me why scientists didn't organize a million person march on Washington to protest the cuts in funding. My response was that due to our increasing specialization, it has become increasingly difficult for us to speak with one voice. By advocating for specific diseases or even specific cancers, we may see short term gains, but to be more effective advocates, we have to get beyond single disease advocacy and recognize that advances in one area can benefit many areas of health.

Impact, not Innovation

Much has been written about promoting innovation and this is one of five criteria in peer-review. I would argue that this criterion should be eliminated from standard grant proposals. I would contend that: 1) most reviewers can't recognize innovation; 2) a truly innovative proposal has a high chance of failure, so in the current funding environment most investigators would not take this risk; 3) there are already grants available for innovative proposals; and 4) whether we like it or not, progress is made by hard work that advances knowledge, with occasional innovations, so if we demand innovation in all we do, we actually impede progress. Instead, we should focus on funding grants that will have an impact or advance a field, while creating environments that foster innovation.

Most major advances in science are based on existing knowledge, with true innovation being quite unusual. I view my own work on the development of imatinib as not particularly innovative, but it has certainly been considered impactful. The reality is that testing drugs to kill cancer cells, even from a novel class of kinase inhibitors, was not innovative. Even the notion of specifically targeting molecular pathogenetic events in a cancer, although unproven in the clinic, was not exactly a novel idea. My work was built upon a logical progression of science. That is not to suggest that there were not insights necessary, hurdles to overcome, or a healthy dose of persistence. It is that we should place more value on impact and results than innovation.

If we examine peer review, it seems unlikely that reviewers can recognize true innovation. The litmus test for innovation is a reaction from reviewers that the experiments will never work. Mario Cappechi's grant to the NIH proposing gene targeting in mammalian

cells was famously rejected due to the view that his proposed experiments were highly unlikely to work. By definition, innovations should be high-risk and high-reward, which means a high likelihood of failure. In our current funding climate, would investigators risk proposing experiments that reviewers think won't work and are highly likely to fail? This seems to be a recipe for a grant not getting funded.

If we recognize that most advances are made by steady progress towards a goal and we eliminated innovation as a criterion from standard grants, we would allow investigators to focus on the impact of their work and how it will advance the field. By continuing to fund innovative grants from a separate pool, we can strike a balance between grants that focus on innovation and grants that are designed to advance a field. I hesitate to use a word such as incremental, which has become a derogatory adjective in the world of peer review, but we have to overcome our resistance to the reality that we need to invest in the hard work and best science that will make continual progress towards a goal. By focusing on goals and outcomes, we can measure progress towards these goals and then we can fund science that allows us to make progress.

We also need to create environments that foster innovation. These environments include ones that focus on outcomes, have a high tolerance for failure, and have some stability in funding. This has been the experience with Howard Hughes Medical Institute funding and is the goal of the Outstanding Investigator Award. In our current funding and promotions and tenure system, our focus is on grants and publications. We all know that if our experiments fail, we won't get a publication, which means we won't get a grant and then our faculty position will be in jeopardy. As such, we have created an environment where failure is feared and with funding constraints, these fears are heightened.

Focusing on Outcomes

Although we must continue to support unfettered basic science, much of what I have been writing about advocates for an increased focus on outcomes. As noted, by outcomes, I don't mean grants or publications; I mean progress towards a goal, advancement of a field, and contributions to scientific understanding. Some of the greatest advances in science have been byproducts from efforts focused on a goal. From the Apollo project, innovations such as the CT scanner, microchips, satellite television, insulating materials, freeze-dried food, and water filtration were created to assist the goal of putting a man on the moon.

Even when we look closer to home, at The Cancer Genome Atlas, improvements in DNA sequencing technology, improved pipelines for alignment to a reference genome, and improved algorithms for data analysis can be attributed in part to this project. The point is that large projects focused on a goal can often be incubators for innovation or unplanned advances. That is not to say that individuals cannot be innovators. It simply is to note that big science does not stifle innovation; it may actually enhance it out of the necessities created by focusing on a goal.

Fifteen years ago, one of my colleagues said that we cannot compare landing on the moon to curing cancer. His argument was that when President Kennedy set a goal of landing on the moon, we had the basic knowledge to accomplish this goal including physics, rocket engines, and even early successes with the space program. With cancer, we did not have these basic tools fifteen years ago. Today, we actually have a much better outline of what it will take - omically-based therapies, immunotherapeutics, and early diagnostics and prevention. And in each category, we have early successes. Sure, there is still much to be learned about the complexity of cancer, but even in the moon landing, there was much to be done. Although I would not advocate that setting a goal of curing cancer in a specified time frame is appropriate, we can certainly set goals for improving five-year survival rates, decreasing the numbers of patients diagnosed with advanced-stage disease or other such outcomes.

Focusing on outcomes forces us to think strategically about how we accelerate progress. It is not about teams versus individuals. It is about how to best fund science to make advances. Is it a mix of individual R01s and teams? What is the right work force? For clinical trials, rather than focusing on how much funding is available, why aren't we focused on what we want our clinical trials to accomplish to have the greatest impact, how the clinical trials effort can be optimally organized, and how much funding is required to accomplish these goals? As an example, we all know that we will need combinations of agents, whether these are molecularly targeted or targeted plus immunotherapeutics. How do we organize pre-clinical efforts to test combinations? How do we create a clinical trials infrastructure to support rapid testing of combinations? And how much funding will this require? Similarly, how do we best structure our clinical trials to analyze success and failure?

As a corollary to focusing on outcomes, we must

have the discipline to carefully manage our portfolio of projects. If a project is not achieving its milestones, we must determine whether impactful progress is being made despite having set unrealistic milestones, or if the funding should be redirected to other, more promising projects.

Team Science

We all know that team sports are not for everyone. By the same token, team science is not for everyone. As we think about accelerating progress, I would argue that we need to enhance our recognition that teams are critically important. The RAS project is an excellent example of bringing a team together to focus on a seemingly intractable problem. In an ideal team effort, individuals with differing perspectives will be engaged who will suggest multiple approaches to solving a problem. Many of these approaches will fail, but the program should be judged based on progress towards the goal of creating a drug for RAS. By the same token, if it becomes clear that this is an intractable problem given our current technologies, then the program should be discontinued. In the event of this apparent "failure", I would argue that the program was a success as an all-out attempt was made to solve an important problem. In the best circumstance, we will end up with a drug for RAS.

In evaluating how best to achieve goals, it is apparent that each approach will have advantages and disadvantages. For example, a major hurdle facing genomically-based therapies is phenotypic validation of mutations. There are many examples of variants occurring in genes known to be oncogenic, occurring at residues predicted to be potentially oncogenic, but in model systems, they have been found to lack transforming abilities. There are three possible approaches to this herculean effort of rapidly screening large numbers of variants of unknown significance. One would be to provide funding supplements to individual laboratories that are expert in a particular gene with a goal of analyzing a specific number of variants per year.

The advantage of this is that individual laboratories would obtain additional funding to support their areas of expertise. The disadvantages are that many labs would shift focus from other work, that there would be no focus on improving output, and it would be unsustainable as more and more variants are identified. A second approach would be to create a program such as CTDD to fund proposals with the most promise of speeding the screening process. The advantage of this is that the best and potentially most innovative science would be funded. The disadvantages are that by funding what we determine to be the best science, we may fund duplicate projects, may not fund projects that are deemed unlikely to work, and might not always hold the grantees to an outcome.

In a team science approach, we would bring together scientists with a diverse set of opinions on what might work; allow them to try a variety of novel technologies, many of which might fail; and hold them to an outcome. The advantages of this are coordination of effort and much easier measurement of progress; however, the project would be critically dependent on a team leader who is open to multiple approaches, team members who are willing to work together, and frequent surveying for new technologies that may improve output.

A Trial of Team Science in Academics

If the Oregon Health & Science University Knight Cancer Institute is successful in meeting the fund-raising challenge given to us by Phil Knight (co-founder of Nike) and his wife Penny, we will have $1 billion to spend on cancer research. As we consider how best to utilize a gift of $1 billion for cancer research, we have decided that we want to create an opportunity for team science in academia. The idea is to bring 20 to 30 scientists together, provide them with HHMI-like funding, and focus the team on a goal. The goal we have set is to improve our ability to accurately detect lethal cancers at the earliest, most curable state, using an understanding of the molecular characteristics of cancers at this stage. The team would be supported by a full complement of shared resources that would allow individual laboratories to be of a relatively small size, but with the intent of maximizing productivity and avoiding unnecessary duplication of effort.

In going back to the elements that create an environment of innovation, our view is that this approach would create such an environment. There are clearly hurdles to overcome within an academic environment, such as teaching, committee work, and promotion and tenure. In establishing our cancer institute, we have worked closely with the leadership of our university and have generated several working principles. For example, there would not be traditional

tenure track appointments; rather, there would be regular reviews of the program and assessment of progress towards goals. In addition, individuals' contributions to the goals of the program would be reviewed, with decisions for contract renewals and promotion based on those reviews.

This type of work environment would not suit everyone, but for the right individuals, we believe we can make significant progress toward our goal and we encourage like-minded individuals to join us.

The author is the director of the Knight Cancer Institute at Oregon Health & Science University, the JELD-WEN Chair of Leukemia Research at OHSU, and is an investigator at the Howard Hughes Medical Institute.

Cancer Survivors Face Greater Economic Burdens, Study Says

By Tessa Vellek

Cancer survivors face higher medical costs and productivity losses when compared to people without a cancer history, according to a CDC study published June 13.

"Cancer survivors face physical, emotional, psychosocial, employment and financial challenges as a result of their cancer diagnosis and treatment," said Donatus Ekwueme, a senior health economist at CDC's Division of Cancer Prevention and Control. "With the number of cancer survivors expected to increase by more than 30 percent in the next decade—to 18 million Americans—medical and public health professionals must be diligent in their efforts to help reduce the burden of cancer on survivors and their families."

From 2008-2011, male cancer survivors had annual medical costs of more than $8,000 per person and productivity losses of $3,700, compared to males without a cancer history at $3,900 and $2,300, respectively.

Female cancer survivors had $8,400 in annual medical costs per person and $4,000 in productivity losses compared to females without a history of cancer at $5,100 and $2,700, respectively.

"These findings suggest the need to develop and evaluate health and employment intervention programs aimed at improving outcomes for cancer survivors and their families," the researchers wrote in their report.

Lost productivity was estimated by assessing employment disability, health-related missed workdays, and days spent in bed due to poor health.

Nearly one-third of cancer survivors experienced limitations in their ability to perform usual daily activities outside of work, and 12 percent had impeded ability to perform mental tasks associated with usual daily activities.

Nearly one-fourth of cancer survivors felt less productive at work. Among employed cancer survivors, cancer and its treatment interfered with physical tasks, 25 percent, and mental tasks, 14 percent, required by the job. More than 42 percent had to make changes to their work hours and duties.

Employment disability accounted for about 75 percent of productivity loss among male and female survivors.

"Society knows that cancer survivors are living longer, but they do not know the extent of the economic hardship cancer survivors are facing. This study sheds light on the magnitude of the economic hardship," Ekwueme said to The Cancer Letter.

"It adds to the growing concern about the costs of cancer care and the huge productivity losses due to increased disruptions in work and daily activities. Now, it is up to society to develop appropriate educational and interventions to aid in transition and retention of cancer survivors in the workplace."

Ekwueme suggested three ways to lessen the economic burden for cancer survivors:

• Public health decision-makers, professional medical organizations, and other stakeholders might want to focus their efforts on factors that can help to reduce the burden of cancer in the general population, including the recurrence of cancer in cancer survivors.

• Encourage primary prevention efforts, such as quitting smoking, being physically active, and maintaining a healthy weight.

• The implementation of the Affordable Care Act could make health insurance more available and affordable and help cancer survivors gain access to health insurance for medical care needs.

The researchers analyzed data from the 2008–2011 Medical Expenditure Panel Survey, sponsored by the Agency for Healthcare Research and Quality and the 2011 MEPS Experiences with Cancer Survivorship Survey to reach their conclusions.

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As Cigars Gain Popularity Among High School Boys, Legacy Urges FDA Regulation

By Tessa Vellek

The number of high school boys who smoke cigars—16.5 percent—is now on par with cigarette use, said the Centers for Disease Control and Prevention.

Among 12th grade boys, cigar smoking was at 23 percent, 3 percent higher than the cigarette use rate, according to the results of the 2013 Youth Risk Behavior Survey, published June 12.

While cigarette smoking has dropped to an all-time low, with 15.7 percent of high school students having smoked cigarettes in 2013, the data shows that cigars and smokeless tobacco rates have stagnated from 2011 to 2013.

Legacy for Health, an advocacy non-profit, is using this new data to urge the FDA to regulate cigars.

This regulation would come in the form of taxes, clean indoor air ordinances, and youth counter-marketing campaigns to reduce youth smoking rates.

"One-third of all youth smokers will eventually die from a disease caused by tobacco and despite restrictions on tobacco advertising to youth, young people are still being exposed to pro-tobacco messaging on a daily basis," Robin Koval, CEO and president of Legacy said in a statement June 12.

"Cigars and smokeless tobacco are every bit as addictive as cigarettes, and this new data from the CDC should serve as an alert to the FDA that its jurisdiction is required to protect our youth from long-term nicotine addiction," Koval said.

Legacy said cigar packaging frequently targets youth—they are sold as singles, come in colorful packages, and have "candy-like" flavors, such as strawberry, grape, and menthol. Legacy is pushing the FDA to ensure cigars are not designed or marketed to appeal to youth.

The agency has proposed to extend its tobacco authority to additional tobacco products, including cigars, e-cigarettes, and hookah. The April 25 proposal is open for public comment until July 9.

The FDA proposes two options for implementing regulation:

• Extend the agency's "tobacco product" authorities to all other product categories, except accessories of tobacco products.

• Extend authorities to all other product categories, except premium cigars and accessories of tobacco products.

"The premium cigars category includes cigars that are used on celebratory occasions only a few times per year," reads the FDA proposal. "It has been suggested that adolescents are not attracted to large and premium cigars, because they are offered for sale at a much higher cost relative to other types of tobacco products and are more difficult to access (e.g., large and premium cigars are typically sold at tobacconists' shops versus convenience stores)."

Youth commonly use manufactured cigars, rather than premium cigars because of ease of access and lower prices, according to a study by the Office of Inspector General for the Department of Health and Human Services.

A White House petition by the International Premium Cigar and Pipe Retailers Association is seeking to exempt premium cigars from the FDA definition of a "tobacco product."

In Brief

Kraft Named Center Director Of Univ. of Arizona Cancer Center

(Continued from page 1)

Kraft will also serve as the Sydney E. Salmon endowed chair, as a tenured professor of medicine in the Division of Hematology/Oncology and as senior associate dean for translational research in the College of Medicine. He is scheduled to take the role of director in September.

He replaces **Anne Cress**, who has served as interim director of the cancer center since July 2013.

At UACC, Kraft will be responsible for the center's $35 million research portfolio and oversight of oncology clinical operations in Tucson, in partnership with the University of Arizona Health Network. He also will oversee the development and implementation of the clinical and clinical research operations at the new UACC facility in Phoenix in collaboration with Dignity Health/St. Joseph's Hospital and Medical Center, which is planned to be completed in summer 2015.

Previously, he served as associate dean for oncology affairs at the Medical University of South Carolina. Kraft led the Hollings Cancer Center's efforts to become an NCI-designated cancer center in 2009.

At MUSC, he also served as a university distinguished professor of medicine and biochemistry and molecular biology, and held the William H. Folk, MD, Chair in Experimental Oncology.

Prior to his appointment at MUSC, Kraft was chief of the Division of Medical Oncology at the University of Colorado Cancer Center; prior to that, he was associate director of the Division of Hematology/Oncology at the University of Alabama at Birmingham.

He is a practicing clinical oncologist with a clinical research focus on sarcoma and genitourinary cancers, and is board certified in internal medicine and oncology.

ST. JUDE CHILDREN'S RESEARCH HOSPITAL's comprehensive cancer center designation was renewed by **NCI**.

The hospital earned the highest possible score of exceptional. St. Jude is the first and only NCI-designated comprehensive cancer center devoted solely to children. St. Jude has been designated as an NCI cancer center since 1977. The hospital was named a comprehensive cancer center in 2008.

A comprehensive cancer center must possess a deep and broad research-based portfolio that extends from the laboratory to the clinic and includes population-based science. Centers must also be actively engaged in professional and public cancer education and outreach.

"The efforts of our more than 160 clinicians and scientists are incredible," said Richard Gilbertson, St. Jude Comprehensive Cancer Center director. "During the last five years, we have made more than 32,500 patient enrollments to clinical studies. In the year prior to our NCI renewal, we ran 166 cancer clinical trials, including 36 brand-new studies."

At St. Jude, the center is organized as five cross-disciplinary, multi-departmental programs aligned to specific diseases and research concepts—Developmental Biology and Solid Tumor Program; Neurobiology and Brain Tumor Program; Hematological Malignancies Program; Cancer Prevention and Control Program; and the Cancer Genetics, Biochemistry and Cell Biology Program.

ASTRAZENECA CAMCAR, S.A., a division of AstraZeneca serving Central American and Caribbean countries, has partnered with **Cancer Genetics Inc.** to provide biomarker-based diagnostic testing for cancer.

Under the terms of the agreement, CGI will perform complex testing for diagnosis and prognosis of cancer patients in Central America and the Caribbean. CGI will work in close conjunction with AZ-CAMCAR on exploring expansion opportunities into additional geographic territories, further oncology categories, and into select oncology trials.

The relationship is expected to concentrate on multiple cancer categories, with lung cancer being an initial area of focus.

MEMORIAL SLOAN KETTERING CANCER CENTER and **Quest Diagnostics** announced a joint collaboration that will focus on gene mutations associated with solid tumors. Financial terms of the agreement were not disclosed.

In the first phase of the collaboration, MSK will provide contextual information about individual mutations identified as part of Quest's OncoVantage test. The test is performed on tumor biopsies and uses next-generation sequencing technology to assess the most commonly mutated exons in 34 genes. The sequencing data, in de-identified form, will be shared with MSK, which will leverage its databases to correlate specific gene mutations to potential therapies and disease progression applicable to that cancer type.

The second phase will involve development of a more far-reaching test by Quest, potentially involving hundreds of genes. The expanded test is expected to launch by the spring of 2015.

MERCK signed collaboration agreement with **Sysmex Inostics GmbH** for the development and commercialization of a blood-based RAS biomarker test for patients with metastatic colorectal cancer.

The agreement was formally signed at a ceremony coinciding with the annual meeting of the American Society of Clinical Oncology in Chicago.

Currently, biomarker testing has been performed with tissue taken directly from the tumor itself, requiring an invasive biopsy. However, recent technological advances have allowed very small amounts of circulating tumor DNA in blood samples to be isolated and tested.

THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY released a compendium of practice tools and resources to help oncologists develop high-quality **cancer survivorship care programs** and improve their existing programs for patients who have completed curative treatment or who have transitioned to maintenance or prophylactic therapy.

The ASCO Cancer Survivorship Compendium serves as a comprehensive source of practical, easy-to-use information on survivorship care not only for the oncology team, but also for all health care clinicians, especially those in primary care.

ASCO's downloadable booklet, "Providing High Quality Survivorship Care in Practice: An ASCO Guide" can assist providers in starting a survivorship program, regardless of practice setting. The guide includes information on the key components of survivorship care, different models of care delivery, and a needs assessment to help users determine which model of delivery may best serve their patients.

THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, the World Health Organization, and the International Association of Cancer Registries developed **guidelines for establishing cancer registries** for low- and middle-income countries.

The publication is available online.

"These guidelines show that cancer registration is always possible, even in low-resource settings," said Freddie Bray, deputy head of the IARC Section of Cancer Information, who coordinated the publication. "With a concerted team effort as well as political commitment, it is possible to successfully develop a population-based cancer registry capable of delivering high-quality data for cancer surveillance and monitoring, and thus support the planning and evaluation of cancer services."

Whereas in high-income countries the expansion of registry data has catalysed changes in national cancer control planning and has played a significant role in determining the cancer burden and its geographical variation, much remains to be done in low- and middle-income countries to ensure a similar development.

"Registry coverage with high-quality data remains well below 10 percent in Africa, Asia, and Latin America, and there is an urgent need to support the initiation, expansion, and development of registries in many low- and middle-income countries," said Roberto Zanetti, president of IACR, an organization with member registries across all continents, and a close partner of IARC. "This new publication will provide invaluable guidance to all those who are seeking to establish or are in the early stages of developing a registry."

THE ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS Certified Clinical Research Coordinator designation is now recognized by the American Nurses Credentialing Center as a valid designation toward meeting staffing requirements of the **ANCC Magnet Recognition Program**.

ANCC recognition of the designation means nurses holding this designation and working in hospital-based research may be included as hospital staff meeting requirements of the Magnet Recognition Program.

According to ANCC, the Magnet Recognition Program "recognizes healthcare organizations for quality patient care, nursing excellence, and innovation in professional nursing practice."

The Magnet program requires a certain percentage of hospital staff hold a current certification from an ANCC-recognized program. Hospitals may also use CCRC-designated nurses as a benchmark toward staffing improvements under the Magnet Recognition Program.

To be recognized by ANCC, certification credentials must be earned from a national certification that meets certain criteria; in particular, the program must be developed using a job analysis and must have an exam developed, maintained and analyzed using best practices in test development and psychometrics.

THE CANCER LETTER received a first place **2014 Dateline Award for Excellence in Local Journalism** from the Society of Professional Journalists June 10. The award recognizes **Paul Goldberg's** series of stories on "Conflict of Interest at MD Anderson Cancer Center" as the winner in the Newsletter, Washington, D.C., category.

"The depth of research is impressive, including digging through documents acquired in public records requests," the jury noted.

The stories recognized by SPJ include:

- May 3, 2013, "AVEO's Tivozanib Sunk by Fundamental Flaw: Higher Overall Survival in the Control Arm."
- May 3, 2013, "AVEO, DePinho Joined at the Hip (Pocket)."
- May 10, 2013, "DePinho Recommended AVEO Stock on CNBC Six Days After FDA Said New Trial Was Needed."
- May 24, 2013, "Translucent Walls, Modern Classics Create 'Corporate Feel' In Office Suite Occupied By Wife of MD Anderson President DePinho."
- Sept. 13, 2013, "DePinho's Wife Was Briefed on AVEO Data 11 Days Before He Touted Stock on CNBC."
- Sept. 20, 2013, "Patient Harm—Including One Death—Cited As Faculty Challenges MD Anderson Leadership."
- Dec. 13, 2013, "CPRIT Official Indicted for Skipping Peer Review."