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To: "Dr. Baruch Fischhoff - Chair, National Academy Committee on Improving Intelligence" <baruch@cmu.edu>

From: Lloyd Etheredge <lloyd.etheredge@policyscience.net>

Subject: 147. Global health and DNI's political opportunity analysis: Fwd: Lancet, "The Case for a Global Rare-Diseases Registry" (8/2/2010) and Time, " Is it Time We Paid More Attention to Rare Diseases" (8/21/2010)

Dear Dr, Fischhoff and Colleagues:

About a year ago I suggested an experiment in cognitive reframing and that Political Opportunity analysis become (alongside risk/threat analysis) a responsibility for the DNI system, with new ideas identified quickly and directly for the President via his daily briefing.

My submission, #4 (9/28/2009, archived online at www.policyscience.net) for your study group urged global health as a new area with emerging, extraordinary opportunities for US leadership, accelerating progress, and strengthening shared humanitarian concerns. As you may recall, I enclosed a copy of a letter of July 21, 2009 to Stephen Groft at NIH re ideas for a Rapid-Learning International Health System and excerpts from the National Intelligence Council's "Strategic Implications of Global Health" analysis in 2008.

These new ideas, which may have seemed unrealistic or ahead of their time a year ago, are ready to get underway. There has been exciting progress in developing this vision and a startup-agenda that can move quickly, using global Internet capabilities, to benefit 250 million people worldwide, including US citizens: I enclose "The Case for a Global Rare-Diseases Registry" that was published in Lancet of 8/2/2010 by C. Forrest, R. Bartek, Y. Rubinstein and S. Groft, and a rapid response and article in Time Magazine (8/21/2010). The global, open science networks can be created by patients and physicians, anywhere, logging onto a Website.

LE

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The case for a global rare-diseases registry

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Rare diseases are a clinically heterogeneous group of about 6500 disorders,[1] and in fewer than 200 000 individuals in the USA.[2] They are commonly diagnosed during childhood, often inherited, and can have deleterious long-term effects. Although any one condition is rare, their cumulative public health burden is substantial, with 6–8% of people having a rare disease at some point during life.[3]

Because of the rarity, no single institution, and in many cases no single country, has sufficient numbers of patients to do generalisable clinical and translational research. Geographic spread of patients has been a major impediment to recruitment into clinical trials. Most rare diseases do not have a specific International Classification of Diseases code, which hampers research that uses existing databases.[3] Before the USA, the European Union, and Asian countries passed orphan-drug legislation more than 20 years ago, the drug industry gave little attention to the development of drugs for these diseases. Although these laws increased the pace of orphan-drug development,[4] most rare diseases still have no medical therapy.

In recognition of these barriers and the moral and public health imperatives to advance knowledge on the best ways to improve the health and wellbeing of patients with rare diseases, recent conferences in the USA[5] and Europe[6] called for wide expansion of access to registries for such patients. The US meeting called for the creation of the infrastructure for a global registry.

Once the population has been defined, various data types can be added. Data can be entered by patients, clinicians, researchers, or be imported from electronic health records. Scientists and drug companies are more likely to research a rare disease if they find a registry in place. Registries enable the formation of infrastructures for various types of research, education, and outcomes improvement (panel).[7,8]

Less than a fifth of rare diseases have registries, and most of these are operated by patients' organisations or researchers.[6] Although most registries are country-specific, there are a few international efforts (eg, in cystic fibrosis[9] and neuromuscular diseases[10]) that are showing the benefits of combining data across international boundaries.

We believe that now is the time to design and develop the infrastructure to foster global rare-disease registries. The increasing mobility of populations and the globalisation of lifestyles and food products make it clear that disease knows no boundaries.[11] Some rare diseases occur so infrequently (<1 per 1 000 000 population) that only by forming international populations can sufficient numbers of patients be accrued. Because funding has been a key obstacle to establishing and maintaining registries, economies of scale that can be developed by forming a global rare-disease infrastructure would improve access to registries for many patients.

Registries are infrastructure, not research projects, and as for so many global concerns, there is no single funding source. A federated model in which several registries for the same disease are linked will most probably be needed to form a global infrastructure. A federated model requires that individual registries are developed or, for those already in existence, transformed to ensure that they are interoperable (ie, data are defined in the same way, use the same standards, and are stored in the same vocabularies).

Panel: **Research functions to enable a patients' registry for rare diseases**

- **Knowledge dissemination:** distribution of information to patients and their clinicians on new therapies, best practices, and safety issues
- **Patients' recruitment:** providing patient-population information for designing trial protocols that optimise size and length of trials
- **Clinical epidemiology:** population descriptive statistics, natural history of disorders, medical practice variation
- **Clinical effectiveness:** evaluation of the effects of preventive, diagnostic, and curative interventions delivered in real-world settings
- **Safety monitoring:** orphan drugs are generally not tested in large phase 3 studies, which makes the need for postmarketing safety surveillance via registries even more important than with conventional drugs[4]
- **Quality and outcomes improvement:** enhancing patients' outcomes by standardising practice and reducing practice variation
- **Genotype/phenotype association studies:** the registry provides phenotypic data which can be linked to genetic and other exposure data
- **Linkage to biospecimens and biorepositories:** to detect phenotypic correlates of cell and tissue biology

For registry developers, there is no established forum for sharing experiences. Each time a new registry is developed, it starts from scratch.[6] Information on best informatics practices and common data templates would go a long way toward reducing the start-up costs associated with developing a registry. Some data elements might be common to all rare diseases (eg, sociodemographics, diagnosis, genetics, growth, medications, services), which raises the possibility of creating a core dataset that can be incorporated into all rare-disease registries.

A single individual, group, or even country will not lead the movement toward formation of a global rare-disease registry. As in the open-source software community, an open-science community for rare diseases is needed. Such a community would ensure that the conditions necessary for data exchange are addressed by defining common datasets, data standards, and vocabularies, and would provide a forum for exchange of experiences and knowledge. The biggest hurdle to our vision of a global registry is not technical, but rather the cultural obstacles to collaboration and data sharing across academic institutions and international boundaries.

Overcoming these hurdles is extremely important. A global infrastructure for a rare-disease registry will inject new energy into the effort to deliver more fully on the promise of orphan-drug legislation. Such a registry will draw new interest in rare diseases from academic researchers and the drug industry because it will enable the design of more effective clinical trials and effectiveness studies and the recruitment of patients much faster and at much lower cost.

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We declare that we have no conflicts of interest.

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TIME Magazine. Saturday, Aug. 21, 2010

Is It Time We Paid More Attention to Rare Diseases?

By Frances Perraudin

When Hannah Ostrea was five months old, she was diagnosed with Gaucher's disease, a genetic condition in which the body lacks the enzyme needed to break down a fatty waste product called glucocerebroside, leaving it to accumulate in the body's organs. The disease is painful, with the excess glucocerebroside impairing mobility and delaying growth. Hannah's form of the disease, Neuronopathic Gaucher's disease, also causes brain damage and eye movement disorders and makes swallowing difficult. Neuronopathic Gaucher's affects less than 1 in 100,000 live births and the life expectancy of a sufferer is between two and 20 years — Hannah is now two. But because the medical community won't dedicate time or money to an illness that affects so few, there is no cure on the horizon. "Unless you have a celebrity who has a personal interest in your disease or you have a 'popular' rare disease ... there are no big foundations, large fundraisers, or even any interest in assistance," says Hannah's mother Carrie. "It's so hard knowing that there is so little research out there for my daughter, and that because of this, we will likely lose her sooner rather than later."

Everybody has heard of the world's biggest killers: cancer, HIV, malaria. But what about Xeroderma pigmentosum, which causes sufferers to react violently to direct exposure to sunlight? Or Jeune Syndrome, a potentially fatal bone-growth disorder that restricts the expansion of organs. An estimated 250 million people worldwide suffer from rare diseases — the term for about 6,500 disorders, each of which, according to the official U.S. definition, affects fewer than 200,000 Americans. Around 8% of people will become afflicted with a rare disease at some point in their lives. Treating these diseases puts a burden on health services and living with them can destroy families — losing a loved one is a tragedy, no matter if it's to cancer or Kawasaki disease, which causes the inflammation of the blood vessels. But because of the rarity of each condition, the number of patients in any one country is too small for experts to use for effective clinical research or raise significant awareness. (See how to prevent illness at any age.)

There have been efforts to address this problem before. The Orphan Drug Act passed in the U.S. in 1983, for example, gives tax incentives to companies that choose to develop such drugs, and grants them the right to sell the drugs without competition for seven years. But this is hardly a comprehensive fix. In the hopes of finally giving rare diseases the attention they deserve, Dr. Christopher Forrest of the University of Pennsylvania and colleagues from the Office of Rare Diseases Research at the National Institutes of Health recently put out a call for the establishment of a global rare-diseases registry. The idea would be to allow patients, clinicians and researchers who are scattered around the world to enter their own data on new therapies and practices, all in

one place. The registry would also provide more accurate patient-population statistics, so that instead of trying to study a handful of sufferers in one country, scientists and drugs companies would have access to information from thousands of people affected by the same rare disorder, making it much easier to conduct research into their causes and cures. "Disease knows no boundaries," Dr. Forrest tells TIME in an email. "Some rare diseases occur so infrequently that only by forming international populations can sufficient numbers of patients be accrued."

Dr. Forrest says the registry's primary goal would be to create an infrastructure to start tackling rare diseases — a necessary first step before trying to raise funding — and prod drug development. Persuading pharmaceutical companies to invest in developing orphan drugs has always been a struggle. Legislation similar to the 1983 U.S. law has been passed in the E.U., Australia and Japan. But developing new drugs can be expensive, and because rare diseases affect so few people, companies see little incentive in doing the necessary research. (See "The Year in Health 2009.")

Recently, though, there have been signs that there could be money in orphan drugs. In early August, multi-national pharmaceutical company Sanofi-Aventis proposed a takeover of Genzyme, the world's third-largest biotechnology company and specialist in orphan drugs. Sanofi reportedly offered $20 billion, but Genzyme is said to be unlikely to accept anything below $22 billion. The move shows that Big Pharma is beginning to see potential in a long-neglected market. "The rare disease market can be profitable in and of itself," says Gary Pisano, a biotechnology industry expert at Harvard Business School. "Genzyme proved this. They were the first to recognize the commercial potential of these markets that had long been ignored because of the apparently small size."

That sounds like good news for rare-disease sufferers. Still, the fact is that profits from orphan drugs are high partly due to the astronomical prices companies can demand for their treatments — with little or no competition, there's no reason for them to keep prices down. Hannah's parents rely on Cerezyme, Genzyme's Gaucher disease drug, to treat their daughter's illness. Costing more than $200,000 for a year's supply, it is one of the most expensive drugs in the world and last year generated sales of $1.2 billion for Genzyme. With Carrie's husband unemployed since February and Carrie having to stay home to look after Hannah, they are burning through their savings to pay for the medication. Billion-dollar deals are no help to them. But if the rare-diseases registry becomes a reality, that could be a big step towards tackling disorders that are devastating for the few who suffer from them. "Deep down I wish the general public would just recognize what families like ours live through on a daily basis," Carries says. "And how rare disease affects each and everyone one of us down to the core."