

Companion Diagnostics for Personalized Medicine
A Critical National Need
for the NIST Technology Innovation Program

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CRITICAL NATIONAL NEED

The proposed topic--“Advancing Diagnostics for Personalized Medicine” --addresses critical national needs with broad societal impact. A September 2008 report titled “Priorities for Personalized Medicine” by the White House Office of Science and Technology Policy (OSTP) underscored the value of personalized medicine both to patient care and our healthcare economy:

The current high level of interest in personalized medicine from a policy perspective is attributable not only to the promise of improved patient care and disease prevention, but also to the potential for personalized medicine to positively impact two other important trends – the increasing cost of health care and the decreasing rate of new medical product development. The ability to distinguish in advance those patients who will benefit from a given treatment and those who are likely to suffer important adverse effects could result in meaningful cost savings for the overall health care system. Moreover, the ability to stratify patients by disease susceptibility or likely response to treatment could also reduce the size, duration, and cost of clinical trials, thus facilitating the development of new treatments, diagnostics, and prevention strategies.¹

The OSTP report further identifies as “Priority Area 1” the need for more federal support for advancing the “Technology and Tools” needed to realize the goals for personalized medicine:

Despite the promise of genomics-based molecular diagnostics to advance personalized medicine, significant challenges remain in validating the genomic/clinical correlations required to advance these products into clinical use. While an increasing number of candidate genetic markers are being discovered, clinical validation of these markers has proceeded at a slow pace. To correct this imbalance between discovery and validation, public and private sector research will need to be coordinated and prioritized more effectively, and the tools required for validation studies will need to be strengthened.

Public/private sector coordination is necessary because the validation of genetic correlations with disease – the key element of translational research in this area – shares many of the attributes of the “development” side of research and development (R&D). Historically, development has been the purview of industry rather than of government-supported academic science, which has instead focused on discovery research. However, **because the validation of genomic correlations with disease is a new, expensive, and high risk R&D area, industry may not be willing to make a substantial investment until a clearer path to validation is developed through the use of public funds. Therefore, in order to move genomic discoveries to practical application, public investment in the translational research necessary to validate genomic/clinical correlations must be increased and also coordinated with industry investment.** (Emphasis added)

Thus, as concluded by the OSTP report, despite the explosive growth of biomarker discovery by academia, these discoveries are for the most part not being effectively translated into products by industry. As a result there are many drugs on the market in need of “companion” diagnostics.

¹ www.ostp.gov/galleries/PCAST/pcast_report_v2.pdf Executive Summary, page 1

Therapies for cancer and other diseases that specifically target aberrant genes or proteins have been a particular focus of leading biotech and pharmaceutical companies over the past ten years. This began in 1998 with the launch of Genentech's breast cancer drug *Herceptin*® that was designed to target the HER-2 (ErbB2) gene product on breast tumor cells. *Herceptin*® is prescribed only to those patients whose tumors overexpress the HER-2 gene. A "companion diagnostic" was introduced to test HER-2 status on tumors before that drug is administered.

At the time the HER-2 drug and diagnostic were launched they were widely hailed in the general and scientific media to be the start of new era of "personalized medicine" that would dramatically improve patient outcomes while reducing healthcare costs. Nearly ten years later, however, only a handful of companion diagnostics have been brought to market, few if any of which have the widespread acceptance of the HER-2 test.² Meanwhile, in the past few years a number of important drugs that target the EGFR (ErbB1) and related pathways have reached the market. These drugs include ImClone's *Erbix* and Genentech's *Tarceva* (see Table below).

Regrettably, most of these newer targeted therapies have been found to benefit only a narrow subset of patients who receive them. For example *Iressa* and *Erbix* are effective in only 10% and 25% of patients, respectively.³ These high failure rates not only cause significant harm to cancer patients, who typically have no time to waste on ineffective treatments, but are a huge drag on the U.S. healthcare economy as well. Biotech cancer therapies often cost \$35,000 to \$55,000 per patient causing significant waste when the wrong treatment regimens are selected for patients. Thus, there is a compelling need for diagnostic tests that can ascertain whether a particular targeted therapy is right for a particular patient before it is prescribed.

The products developed with support from TIP will provide economic benefits far beyond those which accrue to companies which develop them. The enormous cost savings to our nation's healthcare economy in general, and the pharmaceutical industry in particular, from diagnostics that help select, monitor, and personalize drugs for particular patients are significant and well established. For example, the use of genetic testing to personalized dosages of warfarin was estimated to reduce national healthcare spending by \$1.1 billion according to a recent study by the American Enterprise Institute (AEI) and the Brookings Institute. The AEI-Brookings study predicted that formally integrating genetic testing into routine warfarin therapy could allow U.S. patients to avoid 85,000 serious bleeding episodes and 17,000 strokes annually.⁴

With regard to the economic benefits, it is estimated that a validated companion diagnostics would yield about \$ 200 million in annual savings to the U.S. healthcare system. This estimate assumes that approximately 5,000 yearly prescriptions of target therapies (each costing about \$40,000 per year) that ultimately prove ineffective could be avoided with the advent of this test.⁵ Also, if clinicians and patients were informed that an FDA approved therapy would not be effective, they may be more likely to take part in clinical trials of experimental therapies. This would create additional societal benefit as the development of new drugs is typically hampered by the difficulty of enrolling patients in trials.

² Notable examples include the BCR/ABL and c-Kit tests for Novartis' Gleevec.

³ *Business Week*, June 13, 2005 p. 34

⁴ *Wall Street Journal*, Feb. 17, 2007

⁵ We conservatively estimate that we could obtain an adoption rate of about 10,000 tests per year, half of that achieved by Genomic Health only three years from the launch of OncotypeDx. Specific targeted therapies could be ruled out in about half of the tumors samples tested. These estimates do not include economic benefits of other products based on the LES platform.

RECOGNITION OF THE PROBLEM BY THE ADMINISTRATION (INCOMING AND OUTGOING) AND CONGRESSIONAL LEADERS

The proposed topic--“Advancing Diagnostics for Personalized Medicine” – has been a top priority of Congress as well as the outgoing administration. It is also predicted to be a priority of the incoming Obama Administration.

- The aforementioned September 2008 OSTP Report titled “Priorities for Personalized Medicine” recommended that the federal government develop funding programs for academic/industry collaborative projects for validating the clinical utility of molecular diagnostics.
- Last month outgoing Secretary of Health and Human Services Michael Leavitt called upon President-elect Barak Obama to “explore tools of personalized medicine, such as genetic tests and online health records, to mend the U.S. health-care system.” Personalized health care should be an “explicit goal of health care reform,” Leavitt said in a report he called a “note on the desk” to his successor.⁶
- Obama’s presidential campaign issued a press release “Obama-Biden Plan to Combat Cancer” which stated in relevant part “as a Senator, Barack Obama introduced the Genomics and Personalized Medicine Act to create an interagency task force on genomics research, modernize FDA review of genomics tests and expand support to genomics researchers, including funding and creation of a new mechanism to allow researchers across the country to access and analyze genomics research. As president, Obama will continue to support advances in personalized medicine to help ensure early detection and treatment of cancer and other diseases.”
- The Genomics and Personalized Medicine Act of 2008 (H.R.6498) was introduced by Rep. Patrick Kennedy (D – RI) to expand on the efforts of former Senator Barack Obama’s 2007 version of the same bill. Kennedy’s bill adds tax credits and other incentives to encourage companies to invest in personalized medicine products.

TIP FUNDING WOULD UNIQUELY ADDRESS NEEDS NOT MET BY OTHERS

Neither private sector sources (i.e. venture capital or corporations) nor other government agencies (i.e. the NIH) provide the requisite funding to support diagnostics at a level to meet the needs of pressing our healthcare system. There is a need not only for more dollars but also for programs like TIP that encourage partnering and cost sharing between companies large and small.

- **Venture Capital Funding**

Venture capital investment in diagnostics pales in comparison to that in pharmaceuticals and medical devices. According to *BioCentury*, only about three percent of all healthcare VC dollars went to diagnostics companies in 2004. The reasons for this lack of Dx investment activity include historically low margins, commoditization, poor reimbursement, and generally smaller markets compared to pharmaceuticals.⁷ While VC interest in diagnostics began to increase slightly in 2007

⁶ Bloomberg News, Nov. 14, 2008

⁷ Kurtzman, “A Business Model for a New Generation of Diagnostics Companies”, *Biotechnology Healthcare*, Oct. 2005 page 52.

and 2008 the economic downturn has dramatically slowed venture capital overall and this is widely anticipated to remain the case throughout 2009.

- **Corporate Funding**

Unlike large pharmaceutical companies, diagnostics companies have not historically invested heavily in product development. Most of their R&D has focused on their automated instrument platforms. For this reason most diagnostic products are commodities sold by multiple companies resulting in few if any “blockbuster” products. Such an economic framework discourages risk taking, strategic alliances, investment, and partnering. This trend is evolving gradually with companies like Roche Diagnostics, BD, etc. investing more in diagnostic products than in the past. However, cost sharing programs like TIP would likely accelerate this movement.

- **NIH Funding**

NIH funding overwhelmingly supports basic research by academia rather than translational research contributing to commercial products. This has resulted in a huge number of scientific publications relating to biomarkers very few of which have moved into clinical practice. The Small Business Innovative Research (SBIR) program is an exception but this comprises a mere 2.5% of the entire extramural budget. Thus, most SBIR awards are capped at \$750,000. Moreover the SBIR grant reviewers tend to be risk adverse so that transformational product concepts are disadvantaged for funding.

ADVANTAGES OF PROPOSED TIP PROGRAM

It is proposed that a TIP program support the development of “companion” diagnostics to drugs already on the market or in late stage (Phase III) clinical trials.⁸ It is anticipated that most of the applicants would be small or medium sized diagnostics companies in partnership with an academic medical center having access to samples from patients treated with the companion therapy. Cost sharing from small companies would likely come from either (i) a large pharmaceutical company seeking a diagnostic linked to their drug, or (ii) a large diagnostics company seeking marketing rights to the test after it is validated.

Among the key unique features of the TIP program is that the cost sharing requirements should help drive partnering between small, innovative diagnostics companies and large drug and diagnostics companies. “Big Pharma” – Small Biotech Company alliances helped drive the creation of many novel therapies over the past 25 years. This partnering model, unfortunately, has been very rare in the case of diagnostics. The TIP model may cause a paradigm shift in a positive direction.

⁸ The submitter made a similar proposal on November 30, 2004 before the ATP Advisory Committee Meeting where he called for federal matching funds (50:50) for joint ventures between pharmaceutical and diagnostics companies leading to companion diagnostics.