

ASSESSING RISK AND RETURN:  
PERSONALIZED MEDICINE DEVELOPMENT  
& NEW INNOVATION PARADIGM

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## Introduction

In making a credible business case for investors and industry stakeholders to view personalized medicine as a viable business model, we not only must create excitement in the promise of personalized medicine, but also must find viable alternatives in addressing the barriers or risks surrounding the biomedical discovery and development models of today. Some of the risks we identify include IP issues, difficulties in validating targets, ability to rapidly achieve proof of concept, navigating the famed “Valley of Death,” and inefficiencies in the current clinical development process, as well as the need for new industry business models that predict an attractive return on investment. In this paper; however, we limit our discussion to the potential for personalized medicine to create efficiencies in the preclinical and clinical phases of drug innovation and generate economic returns. We also introduce unique industry collaboration mechanisms with nonprofit disease-focused organizations that serve an important role in de-risking aspects of drug discovery and clinical development in their respective disease sectors, as well as bridging early-stage funding needs. These collaborations and de-risking strategies could provide an important model for the further development and growth of the personalized medicine sector.

With respect to definition, we shall use the more general term “stratified medicine,” of which personalized medicine is the individualized member of a spectrum that includes empirical medicine, stratified medicine, and personalized medicine.<sup>1</sup> In the latter two, a biomarker is critical in identifying sub-populations or strata of patients that can benefit from a therapeutic intervention that is related to that biomarker, or develops

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<sup>1</sup> Trusheim, Mark R., Berndt, Ernst R., and Douglas, Frank L., “Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers,” NATURE REVIEWS, March 23, 2007, 1.

a therapy that specifically benefits an individual who possesses that biomarker.<sup>2</sup> A biomarker also may identify strata of patients that might be susceptible to side effects from a particular therapy.<sup>3</sup>

### Current Challenges in Productivity and Investment Returns

The increasing interest and excitement over the promise of stratified medicine is based on the promise of genomics, proteomics, and metabolomics to enable the researcher to identify genes and gene products that are relevant for disease, and to instruct the creation of the best therapies for patients with the respective diseases or side effect susceptibilities.<sup>4</sup> This comes on the heels of the biopharmaceutical industry struggling to meet the increasing demands on its R&D investments while facing declining levels of productivity and innovation, and loss of revenue due to patent expirations. More than three dozen drugs are losing patent protection between 2007 and 2012, with an anticipated \$67 billion loss in sales for the large pharmaceutical companies to generic competition.<sup>5</sup> The industry has responded with pharmaceutical companies increasing R&D spending by 160 percent—from \$15 billion to \$39 billion from 1995 to 2005—and with similar increases in the biotech industry, with a 150 percent increase—from \$8 billion to \$20 billion—in R&D spending during the same period. Meanwhile, submissions for regulatory approval of new drugs and therapeutic indications declined from eighty-eight in 1995 to forty-four in 2004.<sup>6</sup> Innovation in the

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<sup>2</sup> Id.

<sup>3</sup> Id.

<sup>4</sup> Id. at 2.

<sup>5</sup> Ernst & Young, “Beyond Borders,” Global Biotechnology Report, 2008, 3.

<sup>6</sup> Kessel, Mark, and Frank, Frederick, “A Better Prescription for Drug-Development Financing,” *Nature Biotechnology*, 25(8):859-866, August 2007, 859-860.

sector also is continuing to decline, with only seventeen new molecular entities (NME) and two biologics approved in 2007, at a cost of \$2.5 billion per NMEs approved,<sup>7</sup> which is the lowest innovation-to-productivity level since 1983, when twelve NMEs were approved at a cost of \$266 million per NME.<sup>8</sup> (See Figure 1.)



Figure 1: A comparison of biotech and pharmaceutical R&D productivity. Source: Parexel's Pharmaceutical R&D Statistical Sourcebook 2005/2006; Defined Health Analysis. NME, new molecular entity.

The decline in productivity and innovation has increased M&A and partnering activities among large biopharmaceutical companies at a record high in the last few years, with \$150 billion generated through M&A transactions in 2006 and \$22 billion in partnering deals for the same period.<sup>9</sup> The strategy of focusing on a few drug candidates from their combined pipelines, with a focus on producing several “blockbuster” drugs that will generate at least \$1 billion individually in peak annual global sales and be marketable to fifteen million patients or more, has not improved

<sup>7</sup> McCaughan, Michael, “Another Dismal Year for New Drug Approvals.”

<sup>8</sup> Kessel, Mark, and Frank, Frederick, “A Better Prescription for Drug-Development Financing,” *Nature Biotechnology*, 25(8):859-866, August 2007, 859.

<sup>9</sup> Burrill & Company, *Biotech 2007 Life Sciences: A Global Transformation*, 2007, 477.

their productivity levels, resulting in increased delays in development time/costs and increasing cancellations of projects at later stages of development.<sup>10</sup> Additionally, increasing regulatory pressures to conduct more lengthy and complex trials has added to the current \$1 billion<sup>11</sup> in drug development costs, of which half are attributable to the time value of money—that it takes eight to twelve years to get a drug to market.<sup>12</sup> It is also the case that, even after a drug is marketed, 70 percent of the approved drugs do not meet or only match their R&D costs.<sup>13</sup> Thus, with lower efficacy levels (40 percent to 60 percent) of most blockbuster drugs,<sup>14</sup> as well as some high-profile successes of stratified medicines such as Genentech’s Herceptin and Novartis’ Gleevec, the industry is beginning to realize the deficiencies in the economics of the blockbuster business model, which is one of the drivers of increased interest and investment in the development of stratified medicine.<sup>15</sup>

#### A) Early-Stage Funding Challenges in Stratified Medicine Development

The identification of clinical biomarkers or diagnostics linked to gene expression profile of individual or sub-populations of patients is an essential feature of stratified or targeted medicine. This type of research attracts and often is best pursued by small biotech companies. One of the main challenges for these companies lies in the lack of early-stage funding to translate new discoveries into the clinic and, ultimately, to

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<sup>10</sup> The U.S. Government Accountability Office Report: New Drug Development, Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, GAO-07-49, November 2006, 30.

<sup>11</sup> *Id.* at 31; See also, Levine, Daniel S., “Getting Personal,” *The Journal of Life Sciences*, November 2007, 45.

<sup>12</sup> PWC, *Personalized Medicine, The Emerging Pharmacogenomics Revolution*, February 2005, 7.

<sup>13</sup> *Id.*

<sup>14</sup> *Id.*, 2.

<sup>15</sup> Levine, Daniel S., “Getting Personal,” *The Journal of Life Sciences*, November 2007, 45-46.

commercialization. With a narrowing access to public capital and venture capitalists increasingly reticent to invest in early-stage technology companies, smaller biotech companies increasingly are engaging in alternative financing mechanisms that often compromise their value in terms of access to future returns.<sup>16</sup>

Various alternative financing mechanisms, including partnering and out-licensing, sale of royalty streams, and Contract Research Organization (CRO) financings, all include investment capital in exchange for future royalty rights or equity shares in the biotech company.<sup>17</sup> Other innovative financing mechanisms do exist, such as collaborative development financing (CDF), where an investor provides capital and clinical expertise in exchange for licensing of a company's pipeline, while the company maintains the "exclusive right to reacquire the drugs," at prices determined at the time of the agreement.<sup>18</sup> An example of a CDF arrangement is the 2006 Symphony Capitol and Isis Pharmaceuticals ("Isis") collaboration,<sup>19</sup> where Isis received \$75 million to continue the development of its cholesterol-lowering (Phase II) and diabetes drug products (two in pre-clinical) and agreed to an exclusive purchase option for its products at an "annual rate of return that averages 32 percent and is 27 percent at the end of the anticipated" collaboration period.<sup>20</sup> In 2007, Isis exercised its repurchase option, paying Symphony \$131 million. Isis, in turn, executed collaboration agreements with Johnson & Johnson and Genzyme for the three molecules in the contract. These arrangements included

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<sup>16</sup> Kessel, Mark, and Frank, Frederick, "A Better Prescription for Drug-Development Financing," *Nature Biotechnology*, 25(8):859-866, August 2007, 860. See also, NVCA News Release, July 1, 2008: For the first time since 1978, there were no venture-backed IPOs in the second quarter of 2008 as compared to forty-three IPOs in 2008. There were only five IPOs in the first quarter of 2008, compared to eighteen during the first quarter of 2007. NVCA News Release, July 1, 2008.

<sup>17</sup> *Id.*

<sup>18</sup> *Id.*

<sup>19</sup> Isis Pharmaceuticals, "Isis Pharmaceuticals and Symphony GenIsis Enter Into \$75 Million Product Development Collaboration," Isis Pharmaceuticals Press Release, April 7, 2006.

<sup>20</sup> *Id.*

upfront fees in the aggregate of \$370 million with potential milestone payments of nearly \$2 billion.<sup>21</sup> (See Figure 2.)

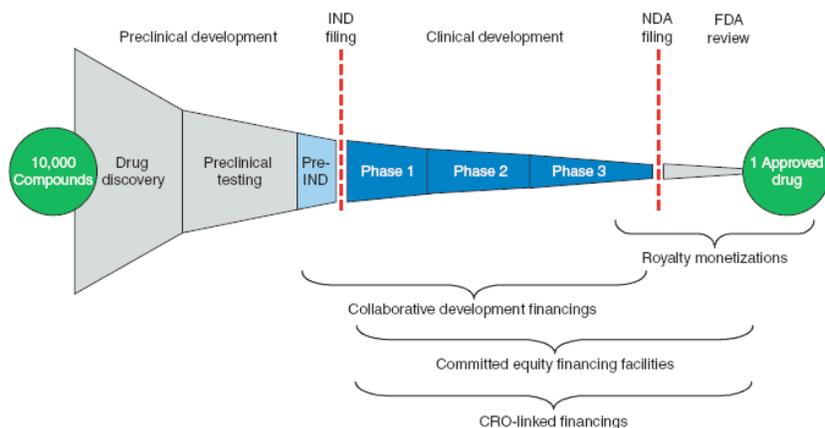


Figure 2: Alternative financing sources for biotech companies<sup>22</sup>

Most of the alternative financing mechanisms, however, are not necessarily accessible for many early-stage companies, as these companies may not have the types of products that meet the returns desired by larger companies and venture capitalists. A case in point is the lack of investment in orphan drugs or neglected disease areas. Aside from Genzyme, which has been one of the few successful orphan drug-focused companies with three drugs on the market, including a \$1 billion-a-year treatment for Gaucher, and Novartis' Gleevec, a treatment for chronic myeloid leukemia with \$2.5 billion in 2006 sales,<sup>23</sup> therapeutic discovery and development for orphan and neglected diseases often have been the bane of nonprofit foundations and patient advocacy organizations, many of whom have increasingly taken on a new role of

<sup>21</sup> Ernst & Young, "Beyond Borders," Global Biotechnology Report, 2008, 45.

<sup>22</sup> Kessel, Mark, and Frank, Frederick, "A Better Prescription for Drug-Development Financing," Nature Biotechnology, 25(8):859-866, August 2007, 862.

<sup>23</sup> Smith, Aaron, "Cashing in on Orphans," CNNMoney.com, March 16, 2007, 1.

bridging early-stage funding and development gaps in disease areas where the patient population often is less than 200,000, the FDA definition of orphan drugs.<sup>24</sup>

To uncover mechanisms by which venture capitalists and biopharmaceutical companies—whose measures of success ultimately are captured in their return on investment (ROI)—could be incentivized to participate in developing stratified medicines, we have looked at the various activities of nonprofit foundations. In our view, these foundations, whose ultimate success is in bringing therapeutics and diagnostics to their patients, increasingly are engaged in “de-risking” strategies. In some cases, their target patient populations fall within the orphan disease category. Their strategies, however, not only fill important funding gaps but also have the objective of increasing the probability of success through their support activities.

#### Venture Philanthropy—Early-Stage Funding/Proof of Concept

Although the nonprofit foundations traditionally provide basic research grants to increase scientific knowledge in their disease sectors, some have since adopted a more investor-like approach—early-stage funding for proof of concept and target validation, as well as project management support and access to their network of scientific experts and research clinics critical in translating discoveries into the clinic.

One example of nonprofit disease organizations that provide early-stage funding for proof of concept and target validation is the Muscular Dystrophy Association (MDA). Through its Translational Research Program (TRP), MDA’s approach is to stratify its patient population based on various sub-sets of the disease, including Duchenne Muscular Dystrophy (DMD), Myotonic Muscular Dystrophy (MMD/DM),

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<sup>24</sup> <http://www.fda.gov/cder/handbook/orphan.htm>.

Fascioscapulohumeral Muscular Dystrophy (FSHD), Spinal Muscular Atrophy (SMA), Pompe Disease, and ALS, and seek to develop targeted therapies for the sub-patient populations.<sup>25</sup> Of the \$32 million in MDA’s 2007 annual R&D budget, \$6 million was dedicated to its largest collaboration effort with ALS Therapy Development Institute (ALS-TDI), a nonprofit corporation, and \$7 million was dedicated to industry collaborations.<sup>26</sup> Muscular Dystrophy Association’s TRP provides four types of funding mechanisms for the industry—IND Planning Grant, Clinical Research Training Grant, Infrastructure Grant, and Corporate Grant—to catalyze early-stage development leading up to INDs and Phase I/II clinical trials.<sup>27</sup> (See details of collaboration deal examples at Figure 3.)

Figure 3: Examples of TRP Industry Grants<sup>28</sup>

Disease Type & Company Grantees	Collaboration Description and Status
DMD/PTC Therapeutics	MDA provided PTC with an initial \$1.5 million grant, enabling the company to begin developing PTC124, a medication with the potential to treat a significant portion of patients with DMD. In July 2008, PTC entered into a collaboration deal with Genzyme, where Genzyme will provide \$100 million to PTC, with potential additional payment options, and will commercialize PTC124 outside the United States and Canada.
Pompe Disease (acid maltase deficiency)/Myozyme (approved 2006) from Genzyme	MDA provided supplemental funding of \$150,000 to cover unreimbursed costs of patients participating in Genzyme’s clinical trials for Myozyme in infantile-onset Pompe disease. In 2007, Genzyme also found Myozyme effective for older children and adults with the disease.

<sup>25</sup> MDA 2007 Annual Report, 4-8.

<sup>26</sup> Interview with Sharon Hesterlee, Vice President of Translational Research, MDA, July 24, 2008.

<sup>27</sup> Gambrill, Sara, “Venture Philanthropy on the Rise,” The CenterWatch Monthly, August 2007, 11.

<sup>28</sup> [http://www.als-mda.org/research/trac/trac\\_fundedproj.html](http://www.als-mda.org/research/trac/trac_fundedproj.html).

ALS Therapy Development Institute (ALS-TDI)	MDA is collaborating with ALS-TDI to comprehensively characterize disease progression in ALS using animal models of neurodegeneration and ALS clinical samples. MDA committed \$6 million annually for three years.
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To qualify for the TRP grants, the collaborating company is required to provide matching grants and agree to a collaboration contract that includes royalty-sharing agreements and march-in rights if the projects fail to meet milestone targets. Similar to a majority of the nonprofit disease organizations, MDA neither takes equity positions in the companies with which it collaborates, nor pursues IP ownership.<sup>29</sup>

Another example of nonprofit disease organizations providing early-stage funding to industry includes the Industry Discovery & Development Partnerships (IDDP) Program of the Juvenile Diabetes Research Foundation (JDRF). IDDP's main focus is to translate scientific discoveries into the clinic and support commercialization of therapeutics to treat type 1 diabetes.<sup>30</sup> Of its \$160 million research budget in 2008, \$16 million will be dedicated to industry partnerships,<sup>31</sup> which is a marked change. Previously, 100 percent of its research funding went to support basic science and exploratory research within academia.<sup>32</sup> To date, IDDP has fostered twenty-four collaborations with industry, totaling \$30 million in IDDP grants.<sup>33</sup> IDDP's development partnerships are generally two- to three-year contracts, and "are intended to provide support for promising mid-stage research programs (i.e., advancement of a pre-clinical-stage program to clinical trials, or "proof-of-concept" Phase II clinical testing of

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<sup>29</sup> Id.

<sup>30</sup> IDDP Fact Sheet, [http://www.jdrf.org/files/General\\_Files/For\\_Scientists/IDDP\\_1\\_pager\\_10\\_29\\_07.pdf](http://www.jdrf.org/files/General_Files/For_Scientists/IDDP_1_pager_10_29_07.pdf).

<sup>31</sup> Interview of Peter T. Lomedico, PhD, Industry Partnerships, JDRF Foundation, July 23, 2008.

<sup>32</sup> Id.

<sup>33</sup> Id.

promising therapeutics”<sup>34</sup>. By funding early-stage testing and validation of research, JDRF’s model of “de-risking” works to make it possible for its industry collaborators to advance their compounds from proof of concept to clinical development, attract additional financing, and eventually secure global licensing and marketing alliances with larger pharmaceutical companies.<sup>35</sup> By funding and providing development support of early trials through IDDP, JDRF also sees this as a way to build evidence in persuading public and private payors to cover these novel technologies.<sup>36</sup> A case in point is IDDP’s collaboration with Tolerx. JDRF provided early-stage, multi-million dollar funding for proof of concept trials in both animal models and early human trials for anti-CD3 antibodies (Otelixizumab) for the treatment of early-stage Type 1 diabetes in collaboration with academic researchers in the United States and Europe.<sup>37</sup> To catalyze further development and commercialization of Otelixizumab, IDDP invested \$3.5 million in an equity stake during Tolerx’s latest round of fundraising to conduct Phase II trials.<sup>38</sup> This is the first project where IDDP has taken an equity position in a collaborating biotech company. As of October 2007, Tolerx entered into a strategic alliance deal with GSK to take the antibody through Phase III trials, with a total deal value potential up to \$155 million.<sup>39</sup> Figure 4 below also exemplifies the significant commitment IDDP has made to companies to support discovery, development, and commercialization of therapeutics and devices for type 1 diabetes.

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<sup>34</sup> Id.

<sup>35</sup> Id.

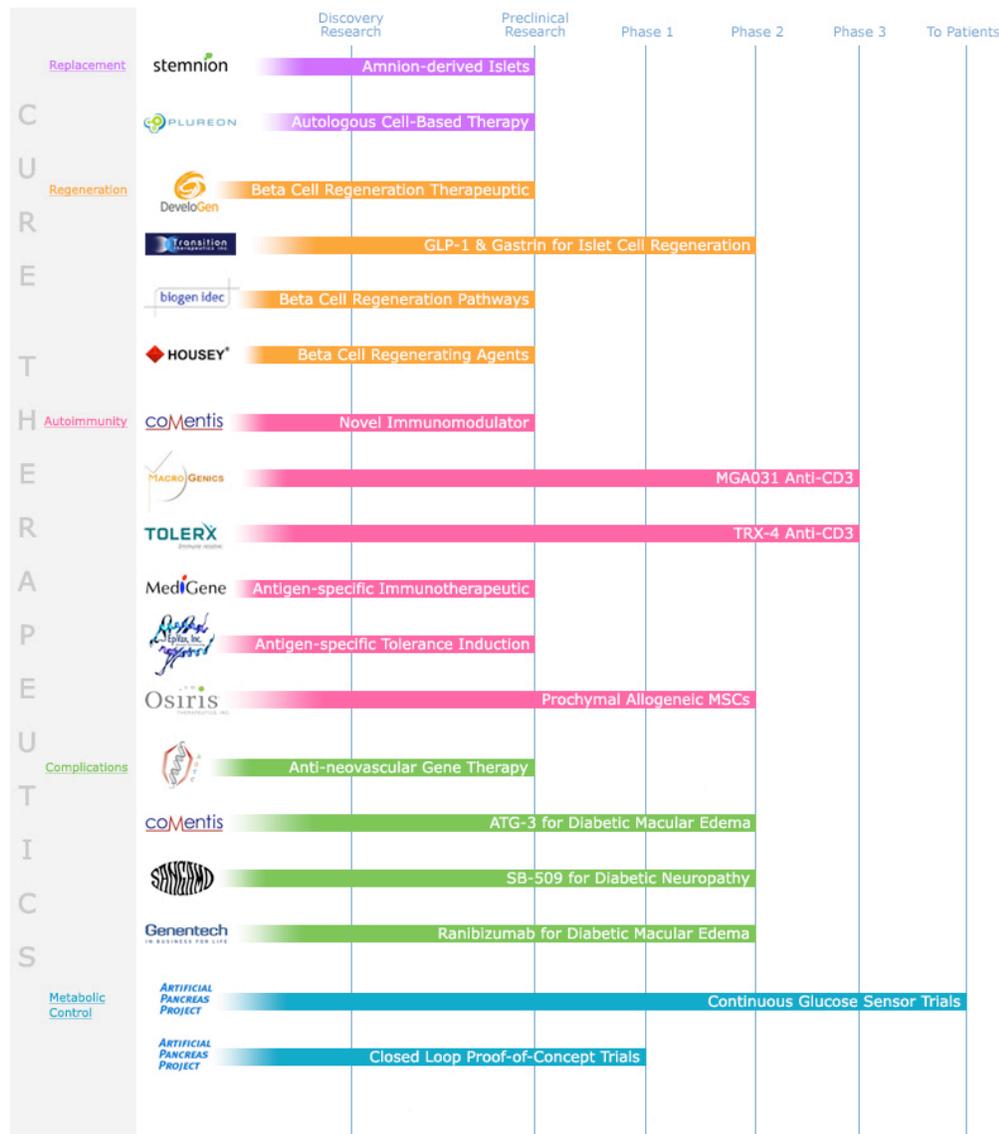
<sup>36</sup> Id.

<sup>37</sup> Interview of Peter T. Lomedico, PhD, Industry Partnerships, JDRF, September 15, 2008.

<sup>38</sup> Id.

<sup>39</sup> Interview of Peter T. Lomedico, PhD, Industry Partnerships, JDRF, July 23, 2008, and September 15, 2008. See also, GSK/Tolerx Press Release: “GlaxoSmithKline and Tolerx Form Collaboration Worth Up to \$155 Million,” October 23, 2007.

Figure 4: IDDP Discovery and Development Pipeline



### Venture Philanthropy and Nonprofit Venture Affiliates

Few nonprofit disease organizations have created wholly owned nonprofit venture affiliates to navigate through the challenges of translating early-stage discoveries into the clinic or bridging the “Valley of Death.” These entities serve as catalysts on various scales, not only by providing variable funding options from annual to multi-year commitments averaging from thousands to multi-millions of dollars, but

also by providing mechanisms to address the development challenges. These include: providing project management expertise and scientific, clinical, and development networks (in some cases CRO outsourcing networks) that can assist the collaborators. In terms of return on investment, most do not take equity positions in the companies they collaborate with; instead, some deals are royalty-based, in which the organizations get a multiple back if the drug is approved and, in some cases, additional compensation for extraordinary sales results. Additionally, in cases where collaboration programs suspend due to milestone failures, some organizations obtain worldwide rights to develop the products with an agreement to negotiate royalties to the original collaborator once their investment is recouped.

An example of a nonprofit disease organization that has created unique project management and target validation mechanisms is the Multiple Myeloma Research Consortium (MMRC), a supporting organization of the Multiple Myeloma Research Foundation (MMRF). Through a collaborative contractual arrangement with its fifteen research centers,<sup>40</sup> the MMRF's strategy is to incentivize biopharmaceutical companies to collaborate on the development of new drugs and therapies. The MMRC's tri-focus on genomics and credentialing of molecular targets, validation of drugs, and its offering of multi-site clinical trial capabilities creates efficiencies that are critical in de-risking early-stage proof of concept and target validation.<sup>41</sup> One of the MMRF's strategies is to

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<sup>40</sup> Fifteen Consortium members include: Dana-Farber Cancer Institute; H. Lee Moffitt Cancer Center & Research Institute; Mayo Clinic Cancer Center; City of Hope National Medical Center; Emory University; Hackensack University Medical Center; Indiana University Simon Cancer Center; Ohio State University Comprehensive Cancer Center; Roswell Park Cancer Institute; Saint Vincent Catholic Medical Centers of New York; University Health Network (Princess Margaret Hospital); University of California, San Francisco; University of Chicago; University of Michigan, Ann Arbor; Washington University in St. Louis. See also, [http://www.themmrc.org/model\\_mmrc.php](http://www.themmrc.org/model_mmrc.php).

<sup>41</sup> Interview with Louise Perkins, PhD, Chief Scientific Officer, Multiple Myeloma Research Foundation, August 13, 2008.

identify genetic complexities of multiple myeloma and to identify molecular targets by analyzing the MMRC's tissue bank and patient data bank on disease onset and progression, with the goal of personalized medicine development.<sup>42</sup> To assist in the process of validating new targets, the MMRC has created screening tools—including a panel of twelve extensively characterized myeloma cell lines with full genetic and biological characterization—to screen new drug candidates.<sup>43</sup> The MMRC also has funded the Multiple Myeloma Genomics Initiative, investing \$8 million in research funding over the past four years to analyze 250 patient tissue samples via gene expression profiling, comparative genomic hybridization and exon re-sequencing.<sup>44</sup> To expedite and create efficiencies in conducting multi-site clinical trials of novel and combination therapies, the MMRC has created uniform contracts, clinical trial agreements, and correlative sciences agreements.<sup>45</sup> (See Figure 5.) To further expedite the process, the MMRC provides supplemental project management to accelerate projects from protocol concept through trial conduct and provides clinical research coordinators for the MMRC members.<sup>46</sup> The MMRF sees its main function as an integrator and facilitator of research and collaboration among biopharma companies with the research centers.<sup>47</sup> Since 2003, the MMRF has helped bring four drugs to market, including Millennium Pharmaceutical's Velcade in 2003, Celgene Pharmaceutical's Thalomid<sup>®</sup> and Revlimide<sup>®</sup> in 2006, and Millennium

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<sup>42</sup> [http://www.themmrc.org/model\\_mmrc.php](http://www.themmrc.org/model_mmrc.php).

<sup>43</sup> Id.

<sup>44</sup> Interview with Louise Perkins, PhD, Chief Scientific Officer, Multiple Myeloma Research Foundation, August 13, 2008.

<sup>45</sup> Id.

<sup>46</sup> Id.

<sup>47</sup> Gambrill, Sara, "Venture Philanthropy on the Rise," *The CenterWatch Monthly*, August 2007, 11.

Pharmaceutical/J&J Pharmaceutical’s Doxil® in 2007,<sup>48</sup> and has supported more than thirty compounds and combinations in trials or pre-clinical studies to date.<sup>49</sup>

Figure 5: MMRC Clinical Trials. MMRC Trials and the year in which they have opened. A total of 15 trials have initiated in the MMRC since 2005. Abbreviations: R: Relapsed; R/R: Relapsed/Refractory; Rev: Revlimid; Dex: Dexamethasone; Vel: Velcae; IST: Investigator-sponsored trial. Unless marked as IST, all trials are company-sponsored. \*\*Trials expected to open by year-end 2008.

	Ph. I/II Novartis LBH589/Velcade	<b>Ph. II HDAC inhibitor/Velcade**</b>
	Ph. I Semafore SF1126	<b>Ph. II mTOR inhibitor/Velcade (IST)**</b>
	Ph. II Proteolix Carfilzomib (R)	Ph. I PDL Elotuzumab/Rev-Dex
	Ph. II Proteolix Carfilzomib (R/R)	Ph. I Celgene CC-4047
Ph. I Nereus NPI-0052	Ph. I Wyeth Torisel/Velcade (IST)	Ph. I PDL Elotuzumab/Vel-Dex
Ph. I Keryx Perifosine/Rev-Dex	Ph. I Ortho Tipifarnib/Velcade (IST)	Ph. I/II Rev-Velcade-Doxil-Dex (IST)
Ph. I Novartis TKI258	Ph. II Novartis LBH589	Ph. Ib Novartis LBH589/Rev-Dex
<b>2005 – 2006</b>	<b>2007</b>	<b>2008</b>

From a funding perspective, 93 percent of the MMRF’s annual budget goes to research and related programming.<sup>50</sup> Of these, in 2007, the MMRF earmarked approximately \$15 million for R&D, with \$2 million allocated for direct funding to biotechs.<sup>51</sup>

One of the leading examples of a nonprofit venture affiliate is the Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), a wholly owned venture arm of the Cystic Fibrosis Foundation (CFF). CFFT’s focus is to develop stratified medicine based on CF-

<sup>48</sup> Velcade in 2003, Thalomid in 2006, Revlimid in 2006, and Doxil in 2007. See also, MMRF Annual Report 2007, 7.

<sup>49</sup> Interview with Louise Perkins, PhD, Chief Scientific Officer, Multiple Myeloma Research Foundation, August 13, 2008. See also, [http://www.themmrc.org/projects\\_clinicaltrials.php](http://www.themmrc.org/projects_clinicaltrials.php).

<sup>50</sup> Interview with Louise Perkins, PhD, Chief Scientific Officer, Multiple Myeloma Research Foundation, August 13, 2008.

<sup>51</sup> MMRF Annual Report, 2007, 5.

related genetic mutations, of which there are 1,400 on a single gene.<sup>52</sup> To date, CFFT has successfully identified and is working on the development of therapies that target the basic defect of the disease, as well as those that will provide better options for disease management. Therapies that target the basic defect are based on various genetic mutations, including Delta F508, a genetic mutation present in 90 percent of cystic fibrosis (CF) patients, and G551D, which is present in 10 percent to 30 percent of CF patients.<sup>53</sup> CFFT's strategy is to invest in early-stage discovery and development. Their funding ranges from \$50,000 to \$25 million, with an average of \$2 million to \$4 million per year, with some multi-year commitments averaging \$15 million to \$20 million.<sup>54</sup> CFFT's successes in aiding drug discovery are measured in terms of increasing its pipeline, which has grown to more than thirty drug candidates.<sup>55</sup> CFFT administers the collaboration contracts based on milestone successes, with pull-out rights for failures.<sup>56</sup> It also invests in a wide range of technologies, from target identification, novel screening platforms, detection of new chemical compounds, and screening of existing compounds and drugs.<sup>57</sup> In terms of return on investment, CFF does not take equity positions in the companies with which it collaborates; instead, some deals are royalty-based, in which CFF may get a multiple back and/or a percent of revenue if the drug is approved and, in some cases, receives additional compensation for extraordinary sales results.<sup>58</sup> Should the development program suspend due to milestone failures, CFF obtains automatic worldwide rights to develop the product with

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<sup>52</sup> Interview with Robert J. Beall, PhD, President and CEO, Cystic Fibrosis Foundation, July 21, 2008.

<sup>53</sup> Id.

<sup>54</sup> Id.

<sup>55</sup> Id.

<sup>56</sup> Id.

<sup>57</sup> Id.

<sup>58</sup> Gambrill, Sara, "Venture Philanthropy on the Rise," *The CenterWatch Monthly*, August 2007, 10.

an agreement to provide some royalties to the original collaborator once CFF's investment is recouped.<sup>59</sup>

An example of CFFT's largest industry collaboration to date includes a multi-year collaboration with Vertex Pharmaceuticals, Inc. (Vertex), in which CFFT provided an aggregate of \$76 million from 2000-2008<sup>60</sup> to support the development of two compounds (VX-770 and VX-809), which target the functional restoration of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the protein responsible for the progression of cystic fibrosis. Through this collaboration, Vertex was able to develop VX-770 from discovery to Phase IIa, where it focused on how VX-770 affects CFTR protein function and clinical endpoints in CF patients with genotype G551D (affects approximately 4 percent of the 30,000 CF patient population in the United States), achieving positive interim results in March 2008.<sup>61</sup> See other examples of CFFT's portfolio in Table 6.

Table 6: Examples of CFFT investments

Collaborating Company	Project Description	CFFT Investment
EPIX Pharmaceuticals, Inc.	Use of EPIX proprietary PREDICT technology to create a computerized 3-D model of CFTR protein, using the model to identify sites within Delta F508 mutation of CFTR and search their library of chemical compounds for a small molecule that may work on those sites. In 2007, EPIX discovered a molecule that, in the lab, restores function to Delta F508 CFTR in cells.	\$52 million including an original \$18 M research award over 3 years and a subsequent discovery and development award over 7 years.
FoldRx	Use of a novel screening platform to	\$22 million over five

<sup>59</sup> Id.

<sup>60</sup> Interview with Robert J. Beall, PhD, President and CEO, Cystic Fibrosis Foundation, July 21, 2008.

<sup>61</sup> Id. See also, Vertex Pharmaceuticals Inc, Press Release on VX-770 Trial Results, March 27, 2008.

Pharmaceuticals, Inc.	detect new chemical compounds that could improve the function of misfolded proteins, like the Delta F508 mutation.	years to use its high-throughput screening platform to discover and develop new compounds.
CombinatoRx, Inc.	Screening approximately 2,000 approved drugs individually or in combination for its impact on correcting Delta F508 in the lab.	Commitment up to \$13.8 million.
Vertex Pharmaceuticals, Inc.	Development of VX-770, its first CFTR modulator clinical compound, which entered Phase II clinical in 2007. Also developing second compound known as “correctors,” VX-809.	\$76 million to date for VX-770 and VX-809.

### Venture Philanthropy and Nonprofit Venture Intermediaries

Few large foundations, like the Gates Foundation through its Global Health Program (GHP), utilize independent nonprofit venture intermediaries to finance and manage the discovery and development of innovative therapies for neglected diseases affecting the developing world.<sup>62</sup> GHP’s goal through its venture intermediaries is to accelerate R&D and provide global access to new vaccines, drugs, and other health tools that combat infectious diseases, including malaria, HIV/AIDS, TB, and pneumonia.<sup>63</sup> The venture intermediaries serve “as a virtual pharma company looking for good ideas, progressing them to the point where proof of concept is achieved,”<sup>64</sup> and de-risking projects to the point that big pharma may be incentivized to collaborate in developing the therapies.<sup>65</sup> GHP is involved in the portfolio management of the venture

<sup>62</sup> [http://www.gatesfoundation.org/nr/downloads/globalhealth/GH\\_fact\\_sheet.pdf](http://www.gatesfoundation.org/nr/downloads/globalhealth/GH_fact_sheet.pdf); Interview of Tadataka Yamada, MD, President Global Health, Gates Foundation, August 1, 2008.

<sup>63</sup> Interview of Tadataka Yamada, MD, President Global Health, Gates Foundation, August 1, 2008.

<sup>64</sup> Id.

<sup>65</sup> Id.

intermediaries, but the intermediary conducts the project management.<sup>66</sup> To date, GHP has committed \$6 billion in global health grants to organizations and researchers worldwide, including \$200 million to Medicine for Malaria Ventures (MMV) over five years.<sup>67</sup>

The venture intermediaries, often called Product Development Public-Private Partnership (PDPs)<sup>68</sup> entities, operate globally with a focus on providing R&D funding and project management expertise in the neglected disease areas such as Malaria and TB.<sup>69</sup> MMV is one of the nonprofit venture intermediaries that the Gates Foundation and GHP funds.<sup>70</sup> MMV's role is to facilitate the discovery and development of innovative anti-malarial drug candidates into clinic.<sup>71</sup> MMV does not conduct discovery or development itself but provides financial and project management support requiring milestone achievements and quick termination rights for those who fail to meet milestones.<sup>72</sup> In return for its investments, MMV often seeks IP rights from the discovery and development projects it funds.<sup>73</sup> In projects that it funds through commercialization, MMV will often negotiate for the delivery of drugs to poor developing countries at "no profit, no loss" basis.<sup>74</sup> It also will retain the ability to license to multiple drug

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<sup>66</sup> Id.

<sup>67</sup> Id.

<sup>68</sup> PDPs are defined as arrangements that innovatively combine different skills and resources from institutions in the public and private sectors to address persistent global health problems. Global Forum for Health Research, Helping Correct the 10/90 Gap, 2008 report at 11.

<sup>69</sup> Id.

<sup>70</sup> Since 1999, MMV has received \$318 million in funds and pledges from private foundations, governments, international organizations, and industry. More than 63 percent (\$200 million) of its pledged funding comes from the Gates Foundation's Global Health Program, and 27 percent (\$86 million) comes from five foreign government agencies and two UN organizations (World Bank and WHO). MMV Annual Report 2007, 46.

<sup>71</sup> MMV at a Glance, MMV: Past, Present, and Future, 2.

<sup>72</sup> Id.

<sup>73</sup> MMV IP Position Paper, [http://www.mmv.org/article.php3?ID\\_article=290](http://www.mmv.org/article.php3?ID_article=290).

<sup>74</sup> Id.

manufacturers.<sup>75</sup> In cases where industry partnership fails during the development phase, MMV will either take full ownership of the IP or require an exclusive, worldwide, transferable license that is royalty free in malaria endemic countries.<sup>76</sup>

In 2007, MMV invested more than \$37 million in nearly forty projects that include four projects in late-stage Phase III clinical trials and three mini-portfolios with GlaxoSmithKline (GSK) (three projects), the Broad Foundation/Genzyme (five projects), and Novartis Institute for Tropical Diseases (NITD)/Novartis (nine projects).<sup>77</sup> Clinical trials MMA supported in 2007 include: Collaboration with Novartis' submission to Swissmedic for approval of its first ACT (Coartem<sup>®</sup> Dispersible); Eurartesim<sup>®</sup> (with Sigma-Tau Pharmaceuticals, Inc.), which received orphan drug designation in the U.S. in 2006 and by the EU in 2008; and MMV/Shin-Poong Pharmaceuticals collaboration for Pyramax<sup>®</sup>. MMV has a wide platform in its collaboration with Shin-Poong, covering two pivotal trials for *Plasmodium falciparum*, trials for *P. vivax*, and also a new formulation specifically for small children.<sup>78</sup>

MMV also has engaged in identifying new targets based on the genome sequence of *Plasmodium falciparum*, the main cause of human malaria, and has collaborated with Novartis and GSK to screen their collection of compounds that may be able to kill the malaria parasite. Out of more than three million compounds tested, more than 10,000 showed interesting activities at low micromolar concentrations.<sup>79</sup> (See Figure 7.)

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<sup>75</sup> MMV IP Position Paper, [http://www.mmv.org/article.php3?ID\\_article=290](http://www.mmv.org/article.php3?ID_article=290).

<sup>76</sup> MMV Annual Report 2007, 18-25.

<sup>77</sup> Id.

<sup>78</sup> Id., 85-25.

<sup>79</sup> Id., 16.

Figure 7: Sample MMV investments in 2007<sup>80</sup>

Collaborating Company	Project Description	Amount Invested in 2007
MMV/Novartis (Coartem <sup>®</sup> Dispersible)	Phase III trial—Development of a pediatric dispersible tablet, Coartem <sup>®</sup> Dispersible, containing a fixed-dose combination of artemether and lumefantrine. (ACT)	\$1.68 million
MMV/Sigma-Tau Pharmaceuticals, Inc. (Eurartesim <sup>®</sup> )	Phase III trial—Fixed-ratio drug combination of dihydroartemisinin and piperazine, being developed to treat uncomplicated malaria.	\$2.85 million
MMV/Shin-Poong Pharmaceuticals, Inc.	Phase III trial—Fixed-dose oral combination of artesunate with pyronaridine. The course of treatment is once a day for three days. Currently carrying out pivotal Phase III studies in <i>Plasmodium falciparum</i> and <i>P. vivax</i> patients to confirm safety and efficacy. A specific pediatric granule formulation also is being tested for safety and efficacy.	\$12 million
MMV/GSK mini-portfolio (five projects)	Engaged in five separate projects ranging from 1) development of next-generation pyridones derivative; 2) development of a second-generation macrolide; 3) identification of additional potent falcipains inhibitors; 4) high-throughput screening assay to study the effect of the entire GSK library of compounds on the growth and death of <i>P. falciparum</i> (To date, the majority of the 1.5 million compounds have been screened in a high-throughput assay, and more than 10,000 hits have so far been identified with interesting activity. The goal for 2008 is to complete the screen, characterize the hits, and use chemo-informatic technologies to cluster them.); and 5) discovery	US \$2.2 million

<sup>80</sup> Id., 18-20.

	program to screen new class of compounds, namely THiQ, that showed promising activity against <i>P. falciparum</i> from its previous Fab1 project.	
MMV/Broad Institute of MIT and Harvard/ Genzyme mini-portfolio (three projects)	Engaged in three projects: 1) screening of the broad compound collection against whole parasite assays with expansion plans in 2008 to include more compounds from the Genzyme library; 2) identification of natural products for malaria treatment; and 3) use of proteomics technology to identify molecular targets. Targets for one of the natural products have been identified, allowing it to be developed for a molecular-based, high-throughput screening (HTS) assay. Focus is to continue identifying more molecular targets that will not only be essential for parasite growth, but tractable in terms of finding small-molecule inhibitors.	\$1.6 million
MMV/NITD/Novartis mini-portfolio (nine projects)	Engaged in nine projects ranging from early-stage research into identifying new targets for liver stages of <i>P. vivax</i> infection, through to optimization of compounds based on artemisinin dimmers. Several projects are moving forward from early-stage hits to lead compounds. One is the chemistry strategy based on successful screening of more than two million compounds from the Novartis compound collection, which led to the selection of more than 6,000 active compounds.	\$589,000

As demonstrated above, the nonprofit disease organizations are having an impact on translating early-stage discoveries to development phases, not only by providing funding for proof of concept and target validation but also by providing project management and a ready-made network of scientific and clinical infrastructures to

expedite and de-risk the development of novel therapies. These approaches are instructive for developing and funding early-stage development models for the stratified medicine sector, but are only part of the picture in making a business case for stratified medicine. We also must assess the clinical trial development risks and how the nonprofit disease organizations may contribute in de-risking clinical development and its applicability to stratified medicine, which will be discussed in the next segment of this paper.

### B) Risks and Impact on Return: De-risking Clinical Trials

The critical part of assessing potential return on biomedical product development hinges on the assessment of risk factors in terms of clinical development costs, time, and success probabilities to get to market.<sup>81</sup> Although most venture capitalists and biopharmaceutical companies use their own valuation models to assess potential investment returns of biomedical products in development, a baseline industry average provides a snapshot of the development risk factors and possible mitigation strategies to employ through unique collaborative models with nonprofit disease organizations.<sup>82</sup>

### Development Risk and Clinical Trial Design

With increasingly complex and chronic diseases as potential targets for new biomedical innovations, the industry is continuing to face decreasing productivity and increasing clinical trial failure rates, adding to the increase in development risks in terms

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<sup>81</sup> Kiev, Ari, "Risks, Reward, and Valuation in Clinical Stage Development: Challenge Your Perspective," Presentation at Investment and Clinical Challenges in the Biotech Industry Conference, Munich, Germany, April 7, 2008.

<sup>82</sup> Ustunel, Sarpel, "How to Put an Accurate Value on Biotech Firms," Professional Investor, October 2005, 20.

of cost/time.<sup>83</sup> Currently, approximately 80 percent of Phase I trials are expected to fail (i.e., they have a 20 percent chance of successfully making it to market), and 70 percent are expected to fail in Phase II,<sup>84</sup> with expected success rates from Phase III to market between 50 percent and 70 percent. New biologic molecular entities have slightly better success rates than those identified for new chemical entities.<sup>85</sup>

These tools will play a significant role in de-risking the drug development process.<sup>86</sup> Continued advancement in new genomics-based technologies and high throughput screening tools will improve researchers' abilities to discover reliable clinical biomarkers that can stratify and enable the discovery of the best therapies for patients.<sup>87</sup> For instance, use of clinical biomarkers early in the clinical trial process could help to decrease costs by identifying better responders, thereby reducing trial sample size to demonstrate efficacy and help to exclude patients early using toxicity biomarkers.<sup>88</sup> In addition, stratifying for key biomarkers early in the trial process not only creates the possibility of shortening end-point observation times, but also creates the ability to gather data to improve the compound or alter the trial design altogether early on, allowing for educated data mining to better define the appropriate patient population.<sup>89</sup>

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<sup>83</sup> The U.S. Government Accountability Office Report: New Drug Development, Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, GAO-07-49, November 2006, 25.

<sup>84</sup> Stewart, Jeffrey J., "Biotechnology Valuations for the 21st Century," Milken Institute Policy Brief, April 2002, 6.

<sup>85</sup> Ustunel, Sarpel, "How to Put an Accurate Value on Biotech Firms," Professional Investor, October 2005, 20.

<sup>86</sup> Trusheim, Mark R., Berndt, Ernst R., and Douglas, Frank L., "Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers," NATURE REVIEWS, March 23, 2007, 3. See also, PriceWaterhouseCoopers LLP, "Personalized Medicine: The Emerging Pharmacogenomics Revolution," Global Technology Centre, Health Research Institute, February 2005, 12-13.

<sup>87</sup> The U.S. Government Accountability Office Report: New Drug Development, Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts, GAO-07-49, November 2006, 27.

<sup>88</sup> Id.

<sup>89</sup> Id.

Additionally, the collection of DNA information from ongoing clinical studies, with patients' consent, also offers the possibility to accelerate future research with increased efficiency.<sup>90</sup> Shorter trials with specific results also have the advantage of expedited FDA reviews, as exemplified by FDA's review and approval of Genentech/Roche's breast cancer treatment, Herceptin, which took six months,<sup>91</sup> or that of Novartis' Gleevec, which took three months. It is anticipated that stratifying patients based on clinical biomarkers may reduce the cost of clinical trials by a factor of two to five, as it would help to narrow the test populations and commercialization time from the current ten to twelve years to five years or less.<sup>92</sup>

#### Time/Cost Correlation

The current industry expectations are the following—in Phase I of the clinical trials, twenty to eighty healthy volunteers are given a new drug compound to test for safety at a cost ranging from \$8,000 to \$15,000 per patient with an average time period of six months to a year.<sup>93</sup> In Phase II, 100 to 300 patients are given the new drug compound to assess clinical efficacy and dosage levels at a cost ranging from \$8,000 to \$15,000 per patient, with an average time period of two to three years.<sup>94</sup> In Phase III, 1,000 to 5,000 patients are tested, often in placebo-controlled, randomized, and double-blinded trials for efficacy and overall risk-benefit assessment at a cost of \$4,000 to \$7,500 per patient. These data

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<sup>90</sup> PriceWaterhouseCoopers LLP, "Personalized Medicine: The Emerging Pharmacogenomics Revolution," Global Technology Centre, Health Research Institute, February 2005, 13.

<sup>91</sup> *Id.* Note: Herceptin is a unique example in that it also relied on a diagnostic test that clearly identified which subset of breast cancer patients would be expected to achieve better results and serious side effects from Herceptin.

<sup>92</sup> PriceWaterhouseCoopers LLP, "Personalized Medicine: The Emerging Pharmacogenomics Revolution," Global Technology Centre, Health Research Institute, February 2005, 14.

<sup>93</sup> *Id.* See also, Jeffrey J. Stewart, "Biotechnology Valuations for the 21st Century," Milken Institute, April 2002, 7.

<sup>94</sup> *Id.*

sets, however, do not provide a clear picture of the real drivers of time/cost correlation. For instance, key drivers of time delay in clinical trials include difficulties in patient recruitment (this causes 33 percent to 66 percent of time delay) and data management (8 percent to 14 percent), as well as difficulty in manufacturing and regulatory/ethics approvals,<sup>95</sup> resulting in upwards of 75 percent of all U.S. trials experiencing delays of one to six months or more.<sup>96</sup> With more than 40 percent to 50 percent of per-patient costs attributable to clinical operations, including project management, monitoring, and regulatory and data management,<sup>97</sup> finding ways to mitigate delays and deploying strategies to increase efficiencies in the clinical process will be critical in decreasing risks associated with development costs/time. (See Figure 8.)

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<sup>95</sup> Kiev, Ari, "Risks, Reward, and Valuation in Clinical Stage Development: Challenge Your Perspective," Presentation at Investment and Clinical Challenges in the Biotech Industry Conference, Munich, Germany, April 7, 2008.

<sup>96</sup> Id.

<sup>97</sup> Id.

Figure 8: Clinical Trial Parameters<sup>98</sup>

**Phase I**

Likelihood of eventual FDA approval: 20%  
Average years to completion: 0.5–1  
Supporting animal studies: ~\$500,000  
Number of clinical-trial subjects: 20–80  
Per-subject cost: \$8,000–\$15,000

**Phase II**

Likelihood of eventual FDA approval: 30%  
Average years to completion: 1.5  
Supporting animal studies: ~\$1 million  
Number of clinical-trial subjects: 100–300  
Per-subject cost: \$8,000–\$15,000

**Phase III**

Likelihood of eventual FDA approval: 67%  
Average years to completion: 3.5 years  
Supporting animal studies: ~\$1.5 million  
Number of clinical-trial subjects: 1,000–5,000 (about 10× the number in phase II)  
Per-subject cost: \$4,000–\$7,500 (half that of earlier per-patient costs)

Venture Philanthropy—Clinical Trial De-risking Mechanisms

In identifying ways to de-risk the time/cost factors in clinical development, one of the emerging models is industry collaboration with nonprofit foundations which, at varying levels, offer mechanisms to expedite and create efficiencies such as readily accessible patient registries and databases, and a broad network of clinical and investigator sites that offer scientific expertise and support.

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<sup>98</sup> Stewart, Jeffrey J., “Biotechnology Valuations for the 21st Century,” Milken Institute Policy Brief, April 2002, 7.

## Venture Philanthropy and Patient Registry/Database

Patient recruitment in clinical trials, especially for specific disease indications, are extremely time consuming and often difficult, adding tremendously to clinical trial time/costs. One of the important de-risking mechanisms provided by the nonprofit disease organizations is access to their network of patient registries and databases. Although most organizations are at various stages of developing their patient registries, Cystic Fibrosis Foundation (CFF) has created an extensive infrastructure to serve this purpose. For instance, CFF accredits more than 115 cystic fibrosis care centers with ninety-five adult care programs and fifty affiliate programs nationwide,<sup>99</sup> creating one of the largest patient registry databases among U.S. foundations, with information about more than 24,000 CF patients receiving care at one of the CF care centers.<sup>100</sup> CFF's database includes not only the patient contact information, but detailed information about genotypes, pulmonary function test (PFT) results, pancreatic enzyme uses, length of hospitalizations, home IV use and complications related to CF, which are critical in assessing trends and in clinical trial designs.<sup>101</sup> The MMRC also has developed a patient database consisting of contact information from 165,000 patients and has launched a new initiative called the patient navigator program to identify and match patients with clinical trials.<sup>102</sup>

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<sup>99</sup> <http://www.cff.org/LivingWithCF/CareCenterNetwork/>.

<sup>100</sup> <http://www.cff.org/research/ClinicalResearch/PatientRegistryReport>.

<sup>101</sup> Id.

<sup>102</sup> Interview with Louise Perkins, PhD, Director of Research, Multiple Myeloma Research Foundation, August 13, 2008.

## Venture Philanthropy and Clinical Trial Networks

One of the critical de-risking mechanisms in terms of development time/costs that many of the nonprofit disease organizations offer is their extensive network of clinical trial sites and expert investigators, as well as information about the ongoing trials in their networks. This offers the ability to conduct multi-site trials with expediency, combined knowledge, and access to quality data from the ongoing trials. Such clinical trial networks also provide the ability to scale up quickly in Phase III studies and, in some cases, conduct Phase IV studies.<sup>103</sup> An important aspect about such a network is the nonprofit disease organizations' collaborative approach to trials, as they often offer centralized review of clinical trial protocols, are able to set common policies to protect patient safety, establish standardized research procedures, share expertise among top researchers, and provide network-wide staff training.<sup>104</sup>

CFF may be one of the leading organizations that, through its Therapeutics Development Network (TDN), offers access to its network of eighteen clinical research centers that specialize in conducting Phase I and II studies for treatment of CF.<sup>105</sup> TDN centralizes and standardizes CF research while providing access to clinical trials data and CF experts through a centralized coordinating center at the Children's Hospital in Seattle, Washington.<sup>106</sup> To enlarge its network, CFF invested \$3 million in 2007 in forty-five new research centers in twenty states nationwide to build an infrastructure to help with patient recruitment and to increase its clinical network.<sup>107</sup> As discussed previously,

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<sup>103</sup> Interview with Robert J. Beall, PhD, President and CEO, Cystic Fibrosis Foundation, July 21, 2008.

<sup>104</sup> Id.

<sup>105</sup> Id.

<sup>106</sup> <http://www.cff.org/research/CFFT/TDN/>.

<sup>107</sup> Interview with Robert J. Beall, PhD, President and CEO, Cystic Fibrosis Foundation, July 21, 2008.

the MMRF also offers a network of fifteen academic centers that collaborate in conducting multi-site clinical trials.<sup>108</sup>

To increase efficiencies, productivity, and sustainability of conducting clinical trials in developing countries, MMV works with a network of international organizations such as the Malaria Clinical Trials Alliance (MCTA), Malaria Vaccine Initiative (MVI), and the INDEPTH Network.<sup>109</sup> MCTA facilitates site preparation for effective conduct of Good Clinical Practices-compliant trials for malaria vaccines and therapies, while supporting the long-term development and sustainability of clinical trial sites in nine countries across Africa (Mozambique, Tanzania, Malawi, Gabon, Nigeria, Ghana, The Gambia, Kenya, and Senegal).<sup>110</sup> MVV also works with the European & Developing Countries Clinical Trials Partnership (EDCTP) to facilitate Phase II and III clinical trials in HIV/AIDS, malaria, and tuberculosis in sub-Saharan Africa.<sup>111</sup>

### Assessment and Recommendation

To reverse the trend of declining productivity and innovation, and embrace the new technological and scientific advances that will allow for safer and more effective treatment of diseases through stratified medicine, industry stakeholders must be open to unique models that could de-risk current drug development processes and increase their combined probabilities of success. Through our discussion, we have identified new collaborative mechanisms with nonprofit disease organizations that can not only help

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<sup>108</sup> See also, [http://www.themmr.org/model\\_mmrc.php](http://www.themmr.org/model_mmrc.php).

<sup>109</sup> <http://www.indepth-network.net/mcta/mctaindex.htm>.

<sup>110</sup> Id.; MCTA was created in 2006 through a \$17 million grant from the Gates Foundation.

<sup>111</sup> EDCTP was created in 2003 as an international organization funded and governed by the fourteen EU Member states, plus Norway and Switzerland, with forty-seven sub-Saharan African countries. See also, [http://www.edctp.org/Frequently\\_Asked\\_Questions\\_FAQ.435.0.html](http://www.edctp.org/Frequently_Asked_Questions_FAQ.435.0.html).

bridge some of the funding gaps in early-stage discovery and development of new technologies, but more importantly, de-risk the clinical process in terms of time and costs.

<b>FOUNDATIONS “DE-RISKING” PROCESSES</b>					
<b>Foundation</b>	<b>Academic Research Networks</b>	<b>Clinical Centers Networks</b>	<b>Tissue Banks</b>	<b>Patient Registries</b>	<b>Project Management</b>
Cystic Fibrosis	✓	✓		✓	✓
Multiple Myeloma	✓	✓	✓	✓	✓
Myelin Repair	✓		✓		
Juvenile Diabetes	✓	✓			✓

In the short term, these mechanisms offer a model for the biopharmaceutical industry in how they can better work with existing nonprofit organizations to capitalize on their offerings. The elements of such a model would include biopharmaceutical companies collaborating with other groups, such as nonprofit foundations, who could establish and manage the programmatic research of networks of academic and investigators from small biotechnology companies, patient registries, and expert clinical centers. In return, large biopharmaceutical companies would provide some funding and commitment to take over the late-stage development of “de-risked” clinical candidates to approval and marketing. There could be several innovative ways to reward the nonprofits for their contribution without violating their mission or 501(c)(3) status.

A critical success factor in stratified medicine is the discovery of the biomarker and/or diagnostic kit. Intellectual property rights can be a potential barrier when there is only one supplier of the diagnostic kit, particularly if that kit has not been approved by regulatory bodies. This presents challenges in reimbursement, as well as potential liability issues if such a kit is used to qualify patients for a drug, and the specificity and sensitivity of the diagnostic test have not been established. This liability exists for both tests of efficacy and susceptibility to side effects. There is, therefore, need to address this downstream issue of potential biomarkers that are discovered in the NIH and other Biomarker consortia.

In summary, this paper focuses on ways to address two of the issues—return on investment and probability of success—that are barriers to the adoption of stratified medicine by large biopharmaceutical companies. The various activities of some foundations serve to identify the relevant patient subgroups and generate data to better qualify potential drug candidates. We call these “de-risking” activities, which not only fill gaps in funding, but improve the probability of success of the drug discovery and development effort. These diseases also are excellent examples where subgroups of patients might be discovered and stratified, and prospective health care—anticipation, prevention, intervention—as described by Dr. Ralph Snyderman, could be pursued on a more rational basis. Thus collaboration between large biopharmaceutical companies and disease foundations provides an interesting model within which several aspects of the development and implementation of prospective health care and stratified medicine might be assessed for technological and economic feasibility.

However, a broader challenge remains in the ability to scale these de-risking mechanisms to a larger set of disease sectors, and on the question of who will bear the cost of creating the necessary infrastructures. One possibility is the U.S. government; as such efforts would be consistent with both the FDA's Critical Path Initiative and the NIH Road Map. We would argue that both the FDA and NIH, under these two initiatives, could encourage the collaborative model suggested in this paper, either by disease category, such as cancer, where there is a known familial or genetic predisposition for the disease. In addition, two areas need to be urgently evaluated or assessed: the barriers that present intellectual property rights pose to adoption of the collaborative model, and the financial value of the varying de-risking strategies that we have discussed. These are the questions we pose today in opening the discussion on how we can make a business case for the growth and adoption of stratified or personalized medicine in the near future.