Analysis In Support Of Medical Research

A Summary of CNA Support to the Brehm Center for Type 1 Diabetes Research and Analysis

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Introduction

In 2006 the University of Michigan (U-M) awarded CNA a two-year contract to establish a systems analysis office at the Brehm Center in the medical school [1]. Our goal was to apply the techniques of systems analysis, in collaboration with traditional biomedical researchers, to increase the pace toward a cure for Type 1 Diabetes (T1D). We carried out a series of research tasks, some focused on analyzing the overall research community, others on providing tools and techniques to T1D researchers. Over the course of the two years, the Brehm Center expanded to include an inter-institutional group of immunologists and beta-cell biologists, the Brehm Coalition. In addition to collaborating with the members of the Brehm Center at the U-M, we also collaborated with the members of the Brehm Coalition as our research warranted.

We began our work with a high-level analysis of the drug development enterprise from pre-discovery to drug delivery by the physician. Based on our analysis of the drug discovery enterprise—participants, timelines, barriers, and incentives—we drew conclusions about the relationship between these factors and the pace of T1D drug development. We were not surprised to find that different incentives among the participants can lead to difficulties working across institutions or across disciplines, or that efforts are underway within the entities to reduce these barriers. We see this in many complex enterprises. However, we were surprised to observe little effort by a defined enterprise leadership working to integrate T1D efforts and few tools to support integration.

Next we examined the economics of T1D in a preliminary effort to establish the “business case for a cure” at the national level. With a yearly cohort of 30,000 new T1D patients, the nation could save $10.6 billion over their lifetime by curing this disease for new onset patients. Furthermore, a cure that targets patients with established T1D, together with new onset cases (a population of roughly 1.1 million patients), would save $423 billion over their lifetime.
When we found that there was no single database for ongoing T1D research funding, we developed one with data provided by the National Institutes of Health (NIH), the Juvenile Diabetes Research Foundation (JDRF), and the American Diabetes Association (ADA). We categorized the on-going research by assigning a set of general labels to each grant—level, focus, discipline, method—in the database and used that information to conduct a high-level examination of funding across the T1D research landscape. Because the T1D community has an incomplete understanding of the underlying causes of the disease, it is not surprising that the largest portion of this funding is going into basic research. The T1D research community can use the landscape database to explore issues of funding level and research focus. In addition, researchers can use the database to identify others working on similar topics easily and to identify gaps in the research effort.

When we understood that the community had a strong desire for a centralized T1D database of digital patient information and a patient sample library, we used our expertise in database design to propose a terminology for a centralized T1D registry (at various levels of complexity). We identified the strengths and challenges of each level and provided some thoughts on how such a registry could be organized and supported by the T1D community.

We also supported one of the primary goals of the Brehm Coalition—to increase collaboration among its members. We developed a tool to quantify increases in collaboration by tracking peer-reviewed publications by coalition members. Using this tool, we can identify improved and new collaborative efforts among coalition members over time and quantitatively show the impact of these collaborations. We also documented lessons learned from other collaborative efforts, and made recommendations on how to incorporate these best practices as similar efforts continue.

Toward the end of our two-year effort, we turned our attention to examining the issue of what research areas still needed to be pur-

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1. Later in this report we describe the meaning of each of these categories and how they help classify, at a general level, the T1D research landscape.
sued and how the tools we developed could be used to facilitate answering that question. We began a proof of concept by looking at several issues the T1D research community had suggested. We approached this work by conducting what we call a meta-systems analysis (MSA). In the MSA, we focus on a narrowly defined, suspected gap in T1D research (e.g., c-peptide standardization) and review the published research on the topic. We then add a summary of the on-going research drawn from the T1D landscape database and clinical trials. This synthesis of past and present research provides a unique look at the research progress on the suspected gap. Moving beyond the proof of concept would have us merging MSAs for a range of specific topics, and in cooperation with the T1D research community, building a prioritized plan for what needs to be accomplished in the way of research for a cure.

In the following summary, we present the details of our analyses, the results and conclusions in the areas described above; for additional details, please consult the referenced CNA reports on each topic.
Understanding the T1D cure enterprise

The T1D drug development and delivery process begins with basic research typically conducted in an academic medical center (AMC) and concludes with a drug being administered to a T1D patient by a medical professional. In this paper we refer to this process as the “T1D cure enterprise.” Our initial work focused on developing a better understanding of the cure enterprise, and the barriers and challenges as they pertained to T1D.

Overview of the enterprise

Figure 1 shows the “as-is” cure enterprise [2].

Figure 1. T1D cure enterprise

<table>
<thead>
<tr>
<th>Basic Research</th>
<th>Drug Development</th>
<th>Approval</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand the disease and identify a target for a cure</td>
<td>Validate drug target, develop &amp; optimize lead, sponsor drug trials</td>
<td>FDA reviews and rules on NDA</td>
<td>Marketing, doctor / patient education, insurance acceptance</td>
</tr>
</tbody>
</table>

Pre-discovery ~ 20 yrs | Discovery / Pre-clinical 3-6 yrs | Clinical Trials 3-6 yrs | FDA review 1-2 yrs |

$?$ | $400 - $800M | $?$ | $?$ |

Pre-discovery ~ 20 yrs | Discovery / Pre-clinical 3-6 yrs | Clinical Trials 3-6 yrs | FDA review 1-2 yrs |

New Therapeutic

Dissemination, acceptance, & follow-up ?yrs
The four phases of the enterprise are shown across the top of Figure 1. In each phase—basic research, drug development, regulatory approval and patient access—different organizations (universities, drug companies, government agencies, patient support groups) and thousands of individuals (patients, researchers, physicians, administrators) are involved in the cure enterprise. Understanding their roles, how they are incentivized, how funding is provided, and how they interact with each other is important to understanding the opportunities, barriers, and challenges associated with the development of effective T1D therapeutics. As an example, at the extreme left of the figure, academic researchers are rewarded by their universities for novel ideas, innovative research results, publications in peer-reviewed journals, and obtaining funding support for their research. Universities are incentivized to train researchers, to advance knowledge for the common good, and by the royalties and potential gains from participating in successful drug development. Drug companies are rewarded financially for successfully bringing a new profitable drug to the market place. A driver for drug companies is a cost-benefit calculation that is carried out at each step in the drug development process. Because costs increase significantly with each step along the translational pipeline, it is in the drug company’s best interest to make good decisions as early as possible in the process.

The triangle on the left-hand side of Figure 1 illustrates the gradual winnowing of ideas as new T1D therapeutics are developed. The basic research phase focuses on understanding the disease etiology and identification of drug targets. It is currently the phase requiring the most work, as the community doesn’t yet fully understand the causes and development of T1D. The transition from basic research to the drug development phase is also of great importance for T1D as this is the interface where the ideas from basic research are translated into a commercially viable new therapy. Although work in both phases can be both publically and privately funded, basic research is often publicly funded and drug development is often privately funded. It has been estimated that each successful therapeutic

2. The cure enterprise shown in Figure 1 can be applied to many different diseases. In this work, where appropriate we made it specific to T1D.
is the result of investigating roughly 10,000 compounds that might be developed for the drug target and an unknown number of ideas that never see the light of day. Developing a single new therapeutic (assuming a disease target is known) generally takes 7 to 15 years and costs in excess of $800 million. Along the way, the drug must successfully clear regulatory milestones, be adopted in the marketplace, and administered to patients. These numbers illustrate the challenges faced by the T1D cure enterprise.

We reviewed and analyzed the challenges and barriers across the T1D cure enterprise. Our work showed us that, within each phase of the enterprise, the challenges and barriers were understood by those participating in that phase and work was on-going to address many of these issues, even if that work at times was not well coordinated across the entire enterprise. For example, the difficulties that young researchers encounter in securing their first independent research grant and its impact on young researcher retention is a concern in the academic community. The funding model for basic research often puts the proposals of established, experienced researchers higher than those of less experienced researchers. Both NIH and the AMCs are attempting to address the issue of whether the science produced by the more experienced researchers should come at the expense of less experienced researchers. Drug companies are constantly looking for ways to reduce the costs of drug development and working with government agencies to improve the drug approval processes. Again, these efforts have met with some success, but, in general, drug development costs are steadily increasing. The FDA has put in place improved processes designed to reduce the time required for drug approval, and academic researchers have suggested less costly trial models, but they have yet to be accepted by the community.

We also undertook case studies of examples of successful drug development for other diseases and other biomedical breakthroughs. In general, we found that these successes were facilitated by centralized integration across the cure enterprise. These examples also benefited from a large commitment on the part of the government, typically due to widespread outcries by the public for a cure. For example, in [3] we discuss the efforts undertaken in the early 1980s to find treatments for HIV. We also noted that many of the downstream barriers to drug development and regulatory approval that
have received considerable press for delaying drugs in the past were overcome during the development of these drugs.

**Enterprise barriers to a cure for T1D**

In the case of T1D, it’s generally agreed in the community that, for now, the search for a T1D cure should focus on basic research and prepare to quickly move any drug targets identified into early drug development. The research community faces basic questions about the onset and natural history of T1D, particularly in its very early stages. Therefore, in the T1D enterprise, the barriers currently of most importance are to the left in Figure 1 and involve the basic research and early drug development communities.

Actions that increase the focus and effectiveness of basic research into the causes of T1D and support the quick translation of drug targets from academia to drug company development could increase the pace of the enterprise. Similarly, lowering the costs of drug development would enable drug companies to stay with possible ideas longer and follow up on more ideas in the development process, thereby potentially increasing the odds of a successful cure reaching the marketplace. Focusing on the interface between the basic research phase and drug development and increasing collaborative opportunities among academia and industry could serve to increase the pace toward a T1D cure.

We found it striking that the T1D cure enterprise lacked a true process leader or integrator. No single organization seemed focused on supporting integration across the entire process nor did the community look to any single organization for such purposes. There are obvious opportunities for integration, such as sharing databases, reducing duplication, collaborating to achieve the necessary skill mix, and for enhanced collaboration among the various funding sources.

We found examples of enhanced collaboration in T1D basic research (the Brehm Coalition is one example where researchers share data and preliminary research results well in advance of possible publications) and examples in other diseases that, although relatively new, seem to be making a difference [3].
In our view, the largest barrier to achieving a cure for T1D is an imperfect understanding of the etiology and basic causes of T1D resulting in a dearth of well understood drug targets for development. As a result we recommend three specific actions that could increase the pace toward a cure:

- Establish a single organization as the process integrator for T1D research in the U.S. This organization should be seen as the facilitator for data sharing and the go-to organization for the status of T1D research progress and opportunities. Either JDRF, ADA, or an NIH agency could possible fill this role as each is already recognized playing a leadership role in the community.

- Develop enhanced processes for bringing together the skills and capabilities for academia and drug companies to increase the development and transition of drug targets for T1D. This could increase the availability of specialized expertise and reduce time to develop T1D drug targets and drugs, especially in the early stages of drug development process.

- Continue to reduce the costs of clinical trials by bringing together academia, drug companies, and the NIH/FDA. The latter stages of the drug development process, the clinical trials, are by far the most costly. By exploring cross-organization opportunities to reduce those costs, ideas might be given more time to develop and be refined in the early stages of drug research.

Because many organizations need to play a role in developing a cure for T1D, and because the autoimmune disease is so complex, the entire enterprise would benefit from improved connections and collaboration across the enterprise. While the three suggestions highlighted above address what we believe to be the largest barriers, work to address downstream barriers could show benefit later in the development of a cure for T1D.

**Economics of T1D**

This work, as is discussed in [4], came out of an early question regarding the costs of T1D that are often overlooked in the discus-
sions about the diabetes epidemic. One motivation for this work was the concern by some in the community that there was not a clear economic case to be made for developing a cure for T1D, in other words the “business case” did not exist. Table 1 shows a summary of the economic costs of T1D in the U.S.

<table>
<thead>
<tr>
<th>Cost component</th>
<th>Per capita costs</th>
<th>Total yearly costs (in billions)</th>
<th>Newly diagnosed cohort of 30,000 (in billions)</th>
<th>Current diagnosed of 1.1 million T1D patients (in billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>6,300 (5,900-7,600)</td>
<td>6.9 (5.6-7.2)</td>
<td>3.3 (2.1 - 4.5)</td>
<td>134.2 (98.1-170.3)</td>
</tr>
<tr>
<td>Indirect</td>
<td>7,200 (6,000-9,300)</td>
<td>7.5 (4.6-10.2)</td>
<td>7.3 (4.3 – 10.4)</td>
<td>289.1 (202.6-375.6)</td>
</tr>
<tr>
<td>Total</td>
<td>13,500 (11,000-17,000)</td>
<td>14.4 (11.5-17.3)</td>
<td>10.6 (7.2 - 14.0)</td>
<td>423.3 (327.2-519.4)</td>
</tr>
</tbody>
</table>

a. Ninety-five percentage confidence intervals are shown in parentheses.
b. Lifetime costs are the present value of the expected stream of costs over the lifetime using a discount rate of 3 percent and T1D mortality rates from the literature.

In an average year between 1999 and 2005, we estimated that $14.4 billion could be attributed to T1D medical costs and lost wages in the U.S. We estimated $6.9 billion in medical expenditures and $7.5 billion in indirect costs were attributable to T1D. Roughly 30,000 people in the U.S. are diagnosed with T1D per year. If the disease could be prevented, the elimination of T1D in this cohort of new patients would save $10.6 billion over their lifetime. Over the lifetime of the current 1.1 million T1D patients, $423.3 billion would be saved if a cure were discovered today.

The analysis above is only the first step toward establishing the “business case” for drug development in T1D. These costs do not include any estimates for the impact of this disease on the families and care givers for these patients. Because many T1D patients are children, these costs are assumed to be significant, but we could find no rigorous way to estimate them.

**Conclusions from the enterprise analysis**

A cure for T1D will be a product of an enterprise that involves public and private funders of research, academic researchers, drug companies, government regulators, physicians, and patients. Our
analysis of the T1D cure enterprise highlighted some of the barriers early in the process that are being and should be addressed.

We believe that fostering collaborative interactions across the T1D enterprise and strategically focusing T1D basic research could be the keys to increasing the pace toward a cure for T1D. An effective integrator of T1D data and research is needed to foster collaboration within the enterprise. In several case studies we reviewed, we found that the government acted in this capacity. In the T1D community there are a number organizations that could take on role thereby fostering increased collaboration across the community.

In addition, efforts should be made to strategically focus and manage T1D basic research. When the costs of the disease are considered, the lack of an obvious strategic focus to T1D research is striking. As we noted, billions of dollars over the lifetime of T1D patients could be saved by a cure for the disease.

Enhancing the interface between basic research and drug development is a key priority. Ensuring that a research finding is more quickly translated into a tangible decision to go forward in drug development, or not, could speed the first steps of the enterprise. Achieving that goal will require close collaboration between the AMCs and the drug companies—a collaboration that, while proving possible benefits, is not without challenges.

Much remains to be done to understand the etiology, initiators, and progress of T1D. Thus, the enterprise must focus much of it efforts on these basic questions. Until significant progress is made on these questions and promising drug targets for T1D are identified, efforts to fix downstream barriers, while important, will not immediately affect the pace toward a cure for T1D.
Analyzing the T1D research landscape

One of the issues we’ve explored in this analysis is the ability of the community to more effectively manage the T1D research portfolio. To optimize the portfolio of T1D research, both at a community level and at an individual level, researchers—individuals and groups—need to better understand how their research fits into the larger research landscape by filling gaps or generating overlaps. In a complex, chronic disease like T1D, with a relatively small patient population, constrained research funding, and questions about the underlying causes of the disease, more effective management of the research portfolio could increase the pace toward a cure for the disease.

To carry out this analysis, we built a database tool of currently funded research proposals from each of the three large funders of T1D research: the National Institutes of Health (NIH), the Juvenile Diabetes Research Foundation (JDRF), and the American Diabetes Association (ADA) [5]. From these three groups, roughly a billion dollars are targeted to diabetes research each year, a portion of which goes to T1D.

Throughout this effort we were challenged by the different formats used by each of the funding organizations and the lack of high-level, community-wide, strategic descriptors to better characterize the ongoing T1D research. The research database at any of these organizations is essentially a collection of grant proposals (including all the information about PIs and institutions) together with the award amounts for each grant. Thus, after merging the three databases, we manually tagged the grants with the following four types of labels so that we could broadly characterize the research across the T1D community:

- Strategic: What pathophysiological stage of T1D is targeted? What is the nature of the work at the most general level?
• Operational: If the work is directly related to T1D, in what area of existing research does the project fall?

• Tactical: What scientific discipline is brought to bear on the research? From what perspective is the research being conducted?

• Method: At what level is the research being conducted (animal model, human, computer model)? Is it work on a tool for researchers rather than research on T1D itself?

Figure 2 shows the specific labels in each of these four categories.

<table>
<thead>
<tr>
<th>Strategic How the research philosophically relates to diabetes</th>
<th>Operational Area of research focus</th>
<th>Tactical Scientific discipline that is brought to bear</th>
<th>Method Type of research end product produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Cause / Identification</td>
<td>Genetics</td>
<td>In vitro</td>
</tr>
<tr>
<td>Prevention</td>
<td>Autoimmune attack</td>
<td>Epidemiology</td>
<td>In vivo</td>
</tr>
<tr>
<td>Treatment</td>
<td>Islet regeneration</td>
<td>Immunology</td>
<td>In silico</td>
</tr>
<tr>
<td>Management</td>
<td>Islet transplantation</td>
<td>Cell Biology</td>
<td>Clinical</td>
</tr>
<tr>
<td>Mitigation</td>
<td>Metabolic control</td>
<td>Neurology</td>
<td>Enabler</td>
</tr>
<tr>
<td>Tangential</td>
<td>Complications</td>
<td>Nephrology</td>
<td>Infrastructure</td>
</tr>
<tr>
<td>Talent / technology</td>
<td></td>
<td>Cardiology</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Ophthalmology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Engineering</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mathematics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Computer Science</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Economics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Education</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nutrition</td>
<td></td>
</tr>
</tbody>
</table>

By including these labels in the T1D research landscape database, not only can we sort the data using key words from the grant descriptions, but we can also sort the data using any combination of these high-level labels. We should also note that adding these labels
to the grant data was very time-consuming as we were forced to categorize each one individually. None of the grants carried these labels. However, by initially including these types of categories in their proposed formats—a very small effort on the front end for each researcher—a single funding organization could easily develop a current database that would enable the community to look across organizations and focus on optimizing the entire research portfolio for T1D.

Optimizing research funding

Using the T1D research landscape tool, we first analyzed research funding from the top down as is shown in Figure 3.

Figure 3. T1D research funding, by agency (2006)

Overall, we found that the T1D community, public and private funders together, spent just over $450 billion on T1D research in 2006. We also found that, for the most part, the funding profile of the ADA and NIH look similar but JDRF funds a larger percentage of treatment projects.³

³ The difference, as seen in the details of the underlying grant data, is due in large part to a very large single grant awarded by the JDRF for treatment research in Australia.
The roughly equal division between basic research and the other categories that are more specifically aimed at patients with T1D (prevention, treatment, mitigation) should not come as a surprise given the lack of knowledge regarding the exact causes of the disease. However, one might ask whether, because the overall funding profiles between the organizations are so similar, is there overlap in the basic research across the community? This type of question can be answered with this database tool. Our reason for presenting these data is to illustrate to the community the utility of our landscape database tool for analyzing T1D funding. The community, working together with the type of analysis presented in Figure 3 (and the details presented below), could better optimize research across the funding organizations, and guard against duplication and lesser funded areas as appropriate in the T1D research portfolio. This analysis, regularly conducted, could be a means of increasing the pace toward a cure for T1D.

Currently the ability of the funding agencies to generate an analysis of the type described here is jeopardized by the lack of high-level descriptors of research in the grant databases and by the lack of standardized funding data across the community [5]. As we started this work, we expected that building the type of database tool described above would be relatively easy and require only a merging of grant data from different sources. Instead, we had to sort and characterize the data supplied by the funding agencies—a time-intensive, manual process. A concerted process improvement in characterizing and cataloging of research, and a concerted effort across the T1D community to standardize the funding data along with this type of analysis could support the community's need to manage T1D research effectively.

## Analyzing research foci

Using the T1D landscape database tool, we can begin to analyze the details that underlie the broad classifications discussed in the previous section.

Figure 4 shows how two of the categories in our T1D research landscape database (strategic and tactical) can be used to highlight how the current research funding is apportioned. Although there are
some areas (in gray) you would not expect to see funded (for example, genetic research is by definition only basic), the figure does reveal areas where the funding is not as plentiful, suggesting further analyses are required to better understand if the funding should be optimized across those areas. For example, the metabolic control category of mitigation is funded at less than $1M (as are a number of other categories). This funding level may be appropriate if the research carried out by others in the community, for example pharmaceutical companies, addresses the relationship between metabolic control and mitigation, or it may warrant further analysis. This tool that supports that type of discussion.

Figure 4. Research funding (strategic and tactical cross tabulation)

As research funds become increasingly constrained, the granting agencies may want to consider more collaborative portfolio strategies. For example, private foundations with the mission to support patients with T1D might focus more on T1D treatments. Public funding could be focused more exclusively on understanding the basics of the disease. These examples are presented to suggest the
type of discussion that would be possible if a common database format and categorization scheme could be adopted across the community. However, absent a tool to illustrate the various funding profiles, this type of analysis is impossible and related discussions are limited.

Illuminating grant networks

In the previous section, we provided an overview of how our T1D landscape database tool could be used by the T1D community to better understand and optimize the entire portfolio of T1D research. We also used the techniques of social network analysis (SNA) to analyze how a researcher could use this same database to optimize his collaborative network or identify gaps in the research landscape, thus highlighting potential avenues for scientific pursuit. Using the grant detail in our T1D research landscape database, a PI (principle investigator) network of researchers working on similar grants can be constructed (Figure 5) [6].
The network map shown above illustrates how our T1D landscape database tool can be used to show linkages between researchers who are working on similar grants, some of whom may be unknown to each other (shown in blue are the members of the Brehm Coalition). The figure was constructed by using a keyword match and scoring algorithm that identified overlaps between on-going research grants.

The idea behind this work was that an analyst and researcher would together use the landscape database tool to better understand the network of potential collaborators or competitors, and how the work of the particular researcher fits into the broader T1D research world.
**Analyzing potential research gaps**

In complex diseases like T1D it can be very difficult to identify research gaps and decide among research priorities. Traditional meta-analyses are helpful but they rely on published research that lags current research by months to years. Because the T1D landscape database provides a window into currently funded research, and a review of trial database can tell us about ongoing and future trials, we developed what we call a Meta Systems Analysis (MSA). A MSA couples a meta-analysis type literature review with a review of the landscape database and review of the trial database to provide us with a fuller picture of the status of research on a particular topic or potential research gap. Our belief is that by coupling various MSAs for a disease we could assist in determining research and funding priorities. This work is still in its early stages, and we’ve only completed a proof of concept.

To illustrate the MSA concept, we quickly summarize our preliminary results for C-peptide in T1D—both measurement standardization and its use as a therapeutic. The idea that C-peptide assay standardization constituted a gap was suggested by a group of researchers as crucial to making progress in treating T1D [7]. We first conducted a literature review that confirmed the fact that C-peptide assay standardization was indeed an area recognized by the community as requiring continued study. Our literature review of C-peptide standardization also revealed the potential of using C-peptide as a therapeutic, an interesting research tangent.

Our further analysis of the literature showed that there are efforts at NIH and within large clinical trial consortia to codify and recommend standardization protocols for C-peptide assays. In addition, the literature on C-peptide as a therapeutic, revealed several promising studies using animal models, and several promising small trials conducted in humans. Thus, although we could identify on-going efforts, we concluded that C-peptide standardization and use as a therapeutic might be good candidates for an MSA issue.

Using the landscape database we found that 25 funded grants that mention using C-peptide assays in the conduct of the proposed research. In those research grants we did not find a single case addressing the standardization issue or evaluating the use of C-peptide
as a therapeutic. Similarly, a review of clinical trials we found 50 clinical trials using the C-peptide assay as a primary or secondary outcome measure and one study evaluating C-peptide as a therapeutic in particular transplant cases. None of the 51 trials addressed the standardization issue.

Our MSAs require further work before they can be published. Because of the importance of C-peptide as an outcome measure for T1D research and the potential value of C-peptide as therapeutic to existing T1D patients we plan to complete the MSA in the near-term. We also plan to apply our MSA methodology to other issues suggested by the community.

Like the T1D landscape, the MSA is an additional analytical tool that can be used to evaluate gaps in the T1D research portfolio. Our view is that this type of analysis could be a first step in systematically addressing potential gaps in the research landscape and beginning to optimize the use of research resources.

**Conclusions from the T1D landscape analysis**

At a high level, the T1D community would benefit from additional community-level strategic thinking about research goals and research tools. As currently implemented, the grant databases maintained by the three largest public and private funders of T1D research cannot conveniently share and characterize research across the community. Thus, an opportunity to better characterize, analyze, and optimize research funding across the entire T1D community is lost. By simply agreeing to assign a set of consistent high-level labels to characterize the research as the grants are awarded, great progress (at relatively small cost) could be made toward characterizing and better understanding of research across the community.

Researchers in the T1D community, like researchers across the biomedical sciences, rely on a number of ways to stay current within their field (journals, conferences, word of mouth, etc). However, with the rapid expansion and specialization of the medical sciences, developing tools to more systematically survey on-going work in a particular area or associated areas could provide a resource to re-
searchers and research institutions. The landscape database tool could also be a useful tool in the creation of coalitions—supporting efforts to form a successful team.

Finally, using the data contained in the T1D landscape database, together with other sources of research information (published literature and clinical trials), allows a synthesis of research information to explore gaps that researchers have identified as being potential areas of focus, area and the investigation of potential gaps. A group of MSAs could allow the T1D community to better prioritize research funding across a range of topics.

Each of these analyses shows the potential for leveraging grant data contained in a communitywide database of on-going, funded research efforts. While each analysis is focused on a different aspect of the community, together they illustrate how the T1D community could better leverage the information they already collect on research funding.
Using systems analysis to support researchers

Much has been written about the need for collaboration in the biomedical sciences as a way to solve complex disease problems. To support the Brehm Center and help facilitate the formation of the Brehm Coalition, we analyzed techniques that could help researchers share data across a community, organize in new and innovative ways, and assess the success of collaborations.

As we carried out this work, the common theme was leveraging data and analyses across the community to optimize the efforts of a particular group of researchers. While biomedical researchers understand in great detail the particulars of their research focus, and while they recognize the need for collaboration, approaching how best to achieve those collaborative goals is not an area that is typically addressed a systematic fashion. The efforts described below include data sharing, learning from successful groups of researchers, and attempting to analyze the progress of collaborative groups.

Providing a shared T1D patient registry

Although our case-study analyses [2, 3] suggested the value of building community-wide research resources for sharing research data across the community, our early analysis of the T1D’s research resources found that for the most part the only resources available to researchers are catalogued genetic information. In multiple discussions throughout this project [7, 8], many stakeholders suggested the need to develop a T1D registry that would be available to researchers across the community. The registry, a shared collection of data on T1D patients (demographic, family, metabolic) possibly linked to a biobank of samples (DNA, blood, etc) from each patient would be a shared resource for the T1D community. Although this idea has a great deal of general support, the myriad registry users and prospective applications of the data, along with the potential technical complexity of the effort, argue against moving forward
without a thoughtful and adaptive design. Thus, we felt it was crucial to agree on a set of concepts and definitions that would allow all interested parties to collectively describe the ultimate vision and goals of such a project and to identify and answer the key questions surrounding this emerging resource. We used Figure 6 as a way to propose a common set of definitions for future discussions.

Figure 6. T1D registry options

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allows easy outreach for education, advocacy support, and trial volunteers</td>
<td>Danger of overusing those on list; doesn’t help with T1D world of knowledge</td>
</tr>
<tr>
<td>Can get natural history of the disease and support patient care</td>
<td>Privacy issues; requires planning for type and format of data collected</td>
</tr>
<tr>
<td>Enables links between genetics and environment/metabolics</td>
<td>Privacy issues; database will be large and complex</td>
</tr>
<tr>
<td>Supports multiple disciplines with access to samples &amp; data</td>
<td>Require long-term $$$, top-down control of data/access required</td>
</tr>
</tbody>
</table>

Although the ideas in Figure 6 have been embraced by the community, and we are aware of one effort to address the top of the pyramid, there is not yet wide support for a larger effort to collect metabolic data and/or genetic and tissue/blood samples. In [8], we outlined our initial thoughts on how the community might move forward in this direction.

Learning from successful collaborations

Although there are many collaborative efforts in the biomedical sciences, and many of the researchers we worked with participated in one or more efforts, we found very few systematic analyses of the practical aspects—successes and failures—of collaborative efforts. To that end, we analyzed a series of case studies (see [2, 3]) to identify lessons that could be applied by a group of researchers hoping to better understand the key elements of successful collaboration. Table 2 summarizes the organizations and medical advances we analyzed in these case studies.
Table 2. Summary of case study analysis

<table>
<thead>
<tr>
<th>Case study</th>
<th>Main points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure Autism Now</td>
<td>Focuses on collecting and centralizing genetic data from those suffering from autism.</td>
</tr>
<tr>
<td>Center Without Walls</td>
<td>Established to increase the pace toward a cure for Multiple Sclerosis (MS). The collaboration was founded on the hypothesis that research could be accelerated by bringing together the top researchers in the field of MS. If they could be motivated to share findings, before waiting for the scientific publication cycle to complete, the pace of research could be accelerated.</td>
</tr>
<tr>
<td>Glaser Pediatric Network</td>
<td>Addresses gaps in its collaborative group by providing additional resources above and beyond those brought by the member labs to enhance the collaborative effort.</td>
</tr>
<tr>
<td>Myelin Repair Foundation</td>
<td>Applies a business model to biomedical research. In addition to recruiting the best researchers in the field, the group is attempting a more strategically focused, cost-benefit informed search for a cure for MS.</td>
</tr>
<tr>
<td>Pritzker Consortium</td>
<td>Pursues a cross-institutional research program. A key feature of its collaborative effort is the need to pool sample data to increase the amount of data to levels required to establish meaningful conclusions.</td>
</tr>
<tr>
<td>Gardasil</td>
<td>After decades of knowledge that cervical cancer was correlated to the HPV virus, causality was proven through a series of studies. A vaccine that prevented the most common forms of the virus was created, developed, approved, and marketed on an expedited timeline.</td>
</tr>
<tr>
<td>Taxol</td>
<td>Once science led to the recognition of the anti-carcinogenic properties of the bark of the yew tree, a powerful treatment for ovarian and breast cancer used an amalgamation of public and private science and funding to maneuver successfully through the pharmaceutical enterprise.</td>
</tr>
<tr>
<td>Human Genome Project</td>
<td>Public and private organizations with diverse interests joined together to complete a medical project both earlier and at less cost than originally thought possible.</td>
</tr>
</tbody>
</table>

In some of the case studies we focused on understanding how groups of researchers collaborate successfully; in others we studied a particular disease therapeutic or scientific breakthrough. As we carried out these analyses, a number of recurring themes emerged.

- A strong scientific plan serves as the collaborative core of a successful collaborative group.
  - A group is most successful when it directs its efforts toward specific and identified gaps in the existing body of research that rely on the strengths of the researchers in the group.
- A well defined management structure and set of ground rules for group governance is crucial to a group’s success.
— Leadership and management are at least as important as ensuring the scientific plan fits the membership and addresses the gaps in the research landscape.

— An outside review board, or other mechanisms to ensure impartial review of the on-going work of the group, provides benefits in terms of prioritizing projects and apportioning funding.

— Establishing objectives and milestones, and applying other methods drawn from the business community, can create a sense of urgency in the group and increase the pace toward the goals.

• Universities are still wrestling with how best to recognize and quantify the contributions of an individual in a group project.

  — Although cooperation is seen as vital for advancing the science, it’s often not seen as vital in advancing one’s career, particularly those early in their scientific careers.

• Advance discussion and planning, focusing on the list of topics below, will enhance the ability of the group to move forward quickly.

  — Embracing technological tools

  — Addressing underlying intellectual property issues

  — Securing reliable and continuous funding

Although researchers are drawn to the science, a successful collaborative endeavor must address a wider set of issues as demonstrated by the list above. While a strong scientific plan is necessarily at the core of a successful group, it is not sufficient for a group’s success. Particularly in groups that cross institution boundaries (academic or otherwise) where differing expectations could easily lead to difficulties within the group, putting in place a management structure to guide the efforts of the group is imperative. Furthermore, being aware of, and addressing these issues up front reduces the probability that they will become stumbling blocks or delay the group’s progress.
Documenting collaboration

Once a group is formed, its progress ideally would be monitored and documented. One way is to measure progress against a set of milestones (as discussed above). Another method is to measure the expansion of the scientific networks as a result of the collaborative effort. We quantified the impact of a collaborative effort on increased scientific networks [9]. Throughout this work, we collaborated closely with the Brehm Coalition of immunologists and cell biologists, an inter-institutional coalition of researchers. Figure 7 shows a collaborative network of the group made by employing the methods of SNA.

Figure 7. Coalition collaborations’ (1997-2007)

a. Analyzed using UCINET v6. The line widths indicate, and the labels show, the number of publications coauthored by the connected individuals.
At the time the analysis was completed, the Brehm Coalition was made up of 10 researchers—6 immunologists and 4 cell biologists. The figure shows the joint publications authored by the coalition members in the five years prior to the formation of the coalition. According to bibliometric theory, the development of new and more tightly focused collaborative efforts, as measured by joint publications, is one of the few ways to quantitatively measure the collaboration across the group. As is evident in the figure, the six immunologists had a relatively active collaborative network prior to the formation of the group. Figure 7 provides a baseline against which future increased collaboration can be measured.

Conclusions

While various research databases exist across the T1D research community, they are typically organized and funded to answer a particular research question. Some researchers have argued that by setting up a communitywide research registry the data across the community could be better leveraged and more efficiently used. However, before creating such a shared resource, the T1D research community would be well served to agree on a common set of goals, potential uses, and terminology to define how such a resource would be structured and what type of data and samples it would contain.

In addition to data sharing, the T1D community and the researchers in that community could better organize and focus their collaborative groups by applying some of the lessons learned from previous efforts. There are numerous successes and failures that when analyzed provide a remarkably consistent set of considerations for a new group to consider as they organize around a scientific question. Quantitatively measuring the progress of the group can also be challenging. Tracking milestones and using bibliometric techniques to track the emergence of new collaborative networks are two different ways to measure progress.

Supporting the development of a community-wide research database, studying collaboration, and using collaborative publications to measure progress are all applications of systems analysis that can work in collaboration with traditional biomedical research tech-
niques and help groups of researchers efficiently accomplish their research goals.
Summary

Two years ago, the U-M asked CNA to participate in an experiment to assess the contributions of systems analysis in collaboration with biomedical researchers. In this report, we’ve highlighted the various ways we applied systems analysis to T1D. Portions of our work focused on ways the community could optimize research funding and identify potential gaps in the T1D research landscape. In other cases, we provided tools and techniques that researchers or groups of researchers could use to augment their traditional research methods and to better organize collaborative efforts.

For T1D, optimizing resources and activities across a community that has no single process leader is a difficult endeavor at best. Creating or appointing a single organization to lead the T1D enterprise is ideal. At the very least, the community could benefit if an organization emerges as the recognized data and analysis integrator. As we’ve demonstrated, there is a wealth of data already in the community that could be used more effectively to inform decisions throughout the T1D community. However, a more focused effort, attempting to use analysis simultaneously across the organizations in the T1D enterprise, could enable the community to more effectively manage their limited resources and better optimize the entire process. Similarly, analyses along these lines could equally be applied to other diseases.

As we’ve shown in this report, systems analysts can augment traditional biomedical researchers and, in our view, provide complementary analytical techniques, results, and recommendations that could be applied to increase the pace toward a cure for T1D.
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