2016 STATE OF THE CURE FOR Type 1 Diabetes
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The JDCA and its employees receive no compensation from the organizations discussed in its report, and seek to avoid relationships with any organizations that could influence its objectivity and independence.
I. Introduction

The 2016 State of the Cure for type 1 diabetes is the fifth annual edition of this report. Like all prior State of the Cure reports, it summarizes progress made during 2016 toward a Practical Cure for type 1 diabetes.

While there are some areas of notable progress in 2016, the overall key finding is largely the same as prior years: there is still a long road ahead. The year ends with only 12 potential Practical Cure projects in human trials, none of which have yet published conclusive results. At the same time, research grant spending by the Juvenile Diabetes Research Foundation (JDRF) reached its lowest level on record at 37% of annual income, down from a peak of 65% in 2008. The American Diabetes Association (ADA) continues to use about 3% of its income to fund T1D research grants.

Meanwhile, the urgency for a real solution for T1D continues to increase. The number of people newly diagnosed with type 1 diabetes continues to rise, year after year, for reasons that scientists are currently unable to explain. Developed countries seem to carry the highest incidence rates, as noted in Chart Ia below. Prevalence estimates suggest that there are 1.5 million people in the United States struggling with type 1 diabetes, and roughly 10 million across the globe. In the US alone, the annual cost of managing the disease is $14.4 billion and expected to rise in the years ahead.

To date, there have been few game-changing breakthroughs since the discovery of insulin in 1922. Many scientists focus their work on an ideal cure that reverses and eliminates the disease, and are often dismissive of those who ask for an expected timetable for completion. The JDCA (Juvenile Diabetes Cure Alliance) argues that it is in the interest of all those living with T1D that the focus shift from an ideal solution to a Practical Cure which would provide a game-changing quality of life improvement for the current generation – the kind that reduces injections, eliminates complications, and maintains regular blood sugars. Imagine what might be in market in the next 15 years if the focus, money, and resources were centered squarely on that objective.

Chart Ia: Estimated new cases of type 1 diabetes (< 15 years) per 100,000 children per year, 2016


“It is in the interest of all those living with T1D that the focus shift from an ideal solution to a Practical Cure.”
II. Donor Priorities (Survey Results)

Most of the donations that fuel the major type 1 diabetes charities come from those most directly connected to T1D: people living with type 1 as well as parents, grandparents, children, and friends. Survey data collected by the JDCA over the past five years consistently shows people most often give their time and hard-earned money with the expectation that their donation will be used to fund cure research.

The JDCA has been conducting surveys of the T1D donor audience to gauge attitudes and intentions for the last five years, and has heard from over three thousand donors in 12 different surveys.

Key Survey Findings:

One key finding that has been consistent throughout all the surveys is that donors overwhelmingly prioritize using their money for cure research. A summary of 2016 donor survey findings follows:

- **92%** of T1D donors state that the main reason they choose to give money and participate in fundraising events is to support cure research, as shown in Chart IIa, highlighting the need for T1D fundraising organizations to make this option readily available.

- **96%** of donors believe cure research should be the number one priority for charities, as shown in Chart IIb. This point is consistent with survey findings from prior years.

- **99%** of donors would give to support Practical Cure research if that option were made easily available to them. The JDCA believes that if non-profits offered this option it would be a win-win and would ultimately increase overall donations. See Chart IIc.

- **83%** said, “100% of the money raised at fundraising walks should be used for cure research.”

- **47%** of respondents said “I will stop participating” or “I am less likely to participate” after learning about the actual amount of money the ADA and JDRF attribute to T1D research. See Chart IIe.
III. Practical Cure Definition

A Practical Cure refers to any type of solution which results in minimizing the disruptive aspects of T1D to achieve a near-normal quality of life. It is distinctly outcome-focused and does not bias toward any type or style of research, provided the objective is delivered.

A Practical Cure is different from a perfect or idealized cure in that it does not represent a reversal or complete elimination of the disease. With a Practical Cure, the disease may remain, but it is managed with the goal of eliminating daily disease management routines and achieving a near-normal lifestyle. **This distinction is important.** Scientists have been pursuing an idealized cure for almost 100 years, but are unlikely to deliver one in time to benefit anyone who is currently living with type 1. Alternatively, there are several projects in human trials that may become a Practical Cure, and there could be many more if resources and funding are allocated toward it.

The Seven Core Criteria of a Practical Cure:

There are seven core criteria that a Practical Cure must fulfill. They are shown in Chart IIIa, and include: sleeping worry-free, no dietary restrictions, minimal monitoring, insignificant side effects, elimination of hypos, and HbA1C readings under 7% with sustainability over time. There are also guidelines for the invasiveness of the type of solution, whether it be pharmacological or surgical.

The 15 Year Time Objective:

Any Practical Cure solution must have a reasonable chance of being available within the next 15 years - in time to transform the lives of people who are currently living with the disease. Considering that on average it requires 10-15 years from the beginning of human trials to receive FDA pre-market approval, research projects that are currently in human clinical trials have the best chance of meeting the timetable. Consequently, this is why the JDCA focuses on human trials.

A defined time objective prioritizes projects that have a reasonable chance of being in market within the next 15 years. The JDCA argues that these projects should be fully-funded and fully-resourced so they move through human trials, and that results, whether positive or negative, are available as quickly as possible.
IV. Practical Cure Pathways

As of November 2016, there are four broad research pathways that have the potential to result in a Practical Cure within the next 15 years. Certain solutions may require a combination of the pathways while others may stand on their own. The four pathways are shown in Chart IVa and discussed below.

1. **Islet Cell Transplantation (including cell supply and cell protection)**

   Islet cell transplantation involves implanting insulin-producing islet cells into a person with type 1 diabetes. It has three major components:
   - **Cell protection:** The islet cells must be protected from the immune attack after they have been implanted in the body. To date, various encapsulation approaches have been tested in humans. Immune-suppressing drugs are an alternative, but side effects still must be reduced.
   - **Cell supply:** The only proven source of islet cells is cadavers, which have very limited availability. Research into deriving a sustainable cell supply from human stem cells has seen promising advances and is currently being tested in three different human trials.
   - **Site selection:** Islet cells require large supplies of oxygen and nutrients to survive. The current protocol is to transplant islet cells into the liver, but this approach yields a very limited cell survival rate. Other sites, including the stomach lining and the area under the skin, are being tested as alternatives.

2. **Immune System Modification**

   Immune system modification stops the body’s immune system from attacking insulin-producing beta cells, either through drugs or stem cell therapy. Currently, human trials are testing the utility of regenerating beta cells alongside immunotherapy in type 1 diabetics with the goal of producing sufficient amounts of insulin. If regeneration proves ineffective, blocking the autoimmune attack would need to be combined with islet cell transplantation. There are currently six active projects in human trials.

3. **Glucose-Responsive Insulin (aka “smart insulin”)**

   Glucose responsive insulin is a type of insulin which chemically-activates in response to blood glucose changes. Once injected, smart insulin remains inactive until blood glucose rises above normal levels. At that point, the chemical component activates the insulin, and once blood glucose returns to normal, the insulin action ceases avoiding low blood sugar. To qualify as a Practical Cure, smart insulin would have to last long enough to eliminate the need for multiple daily injections. There is currently one active project in human trials.

4. **A Device that Mimics the Pancreas (small in size)**

   A device that mimics the pancreas, often referred to as an artificial pancreas, is under development at several commercial and academic centers. The JDCA recently completed a survey asking the T1D community to identify the requirements an artificial pancreas must meet in order to qualify as a Practical Cure. The main factors were reliability, effectiveness at controlling blood sugar, and size. 88% of respondents said an AP device would be a Practical Cure if “it is small enough that you could generally forget that you are wearing it.” None of the current devices being tested in human trials meet this criterion.
Chart IVa:

The **four** practical cure pathways for T1D.

**Practical Cure for T1D**

- HBA1C < 7%
- Minimal Monitoring
- Free Diet
- Eliminate Hypos
- No more than 5 pills per day (if pharmacological)
- Minimal Side Effects
- Less than 10 days in hospital (if surgical)

**Islet Cell Transplantation**
Islet cell transplantation involves implanting insulin-producing islet cells into a person with type 1 diabetes and keeping those cells alive through either encapsulation or immune system modification.

**Immune System Modification**
Therapy to stop immune system from destroying beta cells, including modulating, blocking, and re-training.

**Glucose Responsive Insulin**
“Smart insulin” is injected and chemically activates only in response to changes in blood sugar.

**Devices that mimic the Pancreas**
A device that mimics the pancreas would monitor changes in blood sugar, and calculate and administer insulin without the patient’s input.

Source: JDCA Proprietary Survey of Donor Sentiment, October 2016
V. Practical Cure Projects in Human Trials

As of mid-August 2016, there were 442 active T1D research projects in FDA-approved human trials. These projects touch a wide range of topics related to type 1 diabetes from cure research to mental health, with the largest concentration working to improve glycemic control. Out of the 442 currently underway, only 12 have the potential to be a Practical Cure. See Chart Va.

Chart Va:

Each Practical Cure project is summarized in the Practical Cure charts on the following pages and organized by pathway. Status, phase, and expected completion dates are also indicated. Please note that the JDCA presents these projects without any indication of preference or ranking.

Since the last State of the Cure there is one substantive change in evaluation criteria related to the device pathway based on results from a T1D community survey conducted in 2016 – no current AP devices qualify as a Practical Cure. While there continues to be tremendous enthusiasm and support for the current generation of AP devices being tested, none of these devices are currently minimal enough.

Moving Pieces: Terminated and New Additions

Two projects were prematurely terminated and four new projects have been added. The two projects that were prematurely terminated were a Cyclosporine plus Lansoprazole combination therapy led by Perle Bioscience and a Bio-Artificial Pancreas led by the Imperial College in London. At the same time, four new projects have entered the charts. There is a project in Amman, Jordan seeking to train T-cells, one in Montreal testing a drug combination with INGAP, one in Italy testing a drug combination, and one in New Jersey focusing on modulating regulatory T-cells.
### Practical Cure Pathway: *Immune System Modification with Sustainable Cell Supply*

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<th>PROJECT</th>
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| ATG-GCSF NCT01106157 | University of Florida Gainesville, FL | Drug combination. ATG is aimed at stopping the autoimmune attack, and GCSF is intended to stimulate beta cell regrowth. | Phase I/I  
Estimated completion: January 2018 |
| Stem Cell Educator NCT02624804 | Tianhe Stem Cell Biotech Hackensack, NJ | A patient’s blood is passed through a machine which, through exposure to cord blood stem cells, re-trains the regular blood cells to cease the autoimmune attack. | Phase I  
Pilot study underway  
Estimated completion: January 2018 |
| BCG NCT02081326 | Massachusetts General Hospital Boston, MA | Single drug. Tuberculosis vaccine repurposed to halt autoimmune attack and spur beta cell regeneration. | Phase II  
Recruiting  
Estimated completion: July 2023 |
| Ustekinumab to INGAP NCT02203897 | Jewish General Hospital Montreal, Canada | Drug combination. INGAP-P to induce beta cell regeneration combined with Ustekinumab for autoimmune modulation. | Phase I  
Fully enrolled  
Estimated completion: June 2017 |
| Monorapa (Monotherapy with Rapamycin) NCT02808850 | Fondazione Italiana Diabete Onlus | Drug combination. Rapamycin to modulate immune system by reducing IL2. Vildagliptin to promote beta cell regeneration. | Phase II  
Recruiting  
Estimated completion: December 2018 |
| The T-Rex Study CL503 NCT02691247 | Caladrius Biosciences Sanford Research | Treatment. Use of Tregs to treat immune system imbalances. Endpoint increased pancreatic beta cell function as measured by C-peptide levels. | Phase II  
Recruiting  
Estimated completion: March 2020 |

### Practical Cure Pathway: *Glucose Responsive Insulin*

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| MK-2640 NCT02669735 | Merck Kenilworth, NJ | Responsive and adaptive insulin. Injected under the skin; unique chemical properties activate the insulin when blood sugars rise and halt insulin action when blood sugar drops. Regular injections required. | Phase I  
Completed: results not yet posted |

### Practical Cure Pathway: *Devices that Mimic the Pancreas*

**NO ACTIVE PROJECTS IN HUMAN TRIALS**
# Practical Cure Pathway: Islet Cell Transplantation

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| VC-D1 NCT02239354 | ViaCyte San Diego, CA | Precursor cells, derived from an embryonic stem cell line, mature into functional beta cells when implanted under the skin. Cells are protected by an encapsulation device called Encaptra. | Phase I/II  
Recruiting  
Estimated completion: August 2017 |
| BAIR bio-artificial Pancreas NCT02664309 | Beta-O2 technologies Rosh-Haayin, Israel | Islet cells are encapsulated in a device the size of a hockey puck, which is implanted in the abdomen. Requires daily injections of oxygen into the device. | Phase I/II  
Active, not recruiting  
Estimated completion: March 2018 |
| | Stem Cells Arabia Amman, Jordan | Autologous stem cells are removed, purified, and returned, with expectation that they will evolve into beta cells. Cord-blood derived mesenchymal stem cells are exposed to a patient’s blood cells and returned to the body with intent of stopping the immune attack. | Phase I  
Active, not recruiting  
Estimated completion: January 2019 |
| Monolayer Cellular Device NCT00790237 | Cliniques universitaires Saint-Luc-UCL Bruxelles, Belgium | Islet cells are encapsulated in an alginate device (patch size of 1-3 cm) and transplanted subcutaneously. Phase 1a of testing is accompanied by immunosuppressive drugs Phase 1b is free of immunosuppression. | Phase I  
Completed: results not yet posted |
| Diabecell NCT01798228 | Diatranz-Ortsuka Ltd. Auckland, New Zealand | Porcine islets are encapsulated in alginate microcapsules, which are implanted in the abdomen. | Phase II  
Completed: results not yet posted |

## Abandoned Since Last Update

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<tr>
<th>PROJECT</th>
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<tbody>
<tr>
<td>Cyclosporine + Lansoprazole / Omeprazole NCT01762644</td>
<td>Perle Bioscience Philadelphia, PA</td>
<td>Drug combination. Cyclosporine is supposed to stop the autoimmune attack; Lansoprazole or Omeprazole is supposed to stimulate beta cell regrowth.</td>
<td>ABANDONED</td>
</tr>
<tr>
<td>Bio-Inspired Artificial Pancreas NCT02395265</td>
<td>Imperial College London, U.K.</td>
<td>Same as above.</td>
<td>ABANDONED</td>
</tr>
</tbody>
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## Emerging Practical Cure Projects

Outside of the projects included here, there are many more that are not yet ready for human testing. While the JDCA follows these projects with great interest, it will only begin to cover them comprehensively once they move into human trials, which the JDCA hopes will be in the imminent future.
VI. Cure Research Funding

The three organizations that fund most of the type 1 diabetes research conducted in the United States are the ADA, JDRF, and NIH (National Institute for Health). The ADA and JDRF are non-profit organizations unaffiliated with the government, while the NIH is a US government agency.

The ADA and JDRF each raise roughly $200 million per year, a portion of which is used to fund research. NIH has earmarked $150 million per year to be used for type 1 diabetes, but based on NIH projections, this figure is expected to decline in the years ahead. The following sections outline noteworthy developments of each organization during the past year.

JDRF:

Founded in 1970 with a mission of finding a cure for T1D, JDRF has grown to become the largest and most influential type 1 diabetes organization in existence. With chapters throughout the world and strong relationships with all the principle investigative research centers, JDRF is uniquely positioned to bring about a major breakthrough.

- Until 2008, expenditures were consistent with the organization’s mission, with roughly 60% of all income used to fund research grants. After 2008, that percentage has steadily declined to 37% in 2015, an all-time low. See Chart VIa.

Chart VIa:
JDRF Research Grants as a Percent of Annual Income

- As research dropped to a record low, spending on education reached a record high, as did the internal costs associated with giving grants. Education spending peaked in 2015 at $53 million, nearly 1/3 of annual income.

“With chapters throughout the world and strong relationships with all the principle investigative research centers, JDRF is uniquely positioned to bring about a major breakthrough.”
Internal costs associated with giving research grants also reached a record high in 2015, rising dramatically from the early 2000s. In 2007, costs associated with giving research grants were six cents per grant dollar. By 2015, it rose to 27 cents per research grant dollar. See Chart VIc.

During 2015, JDRF posted an annual income of $197 million. The 37% attributed to research addressed a range of topics including cure research, the artificial pancreas, treatment, prevention, and complications. See Chart VId.

113 organizations received grants from JDRF providing support for 387 individual research projects. The five largest recipients collected 31% of the total research grant funding. See sidebar.
ADA:

The ADA was founded in 1940 with the mission of finding a cure for all types of diabetes, unlike JDRF which focuses on type 1 only. The ADA has evolved over time to become one of largest diabetes organizations in the world.

- During the 11 years that the JDCA has been tracking the ADA, research spending is down compared to the early 2000s, but is relatively constant in terms of the proportion of income. See Chart VIf.

In 2015, the ADA posted revenue of $182 million, down from $201 million in the prior year, raised primarily from donations and magazine proceeds. Just 3% of that income was allocated to type 1 research. In addition, the ADA does not fund Practical Cure research of any kind. See Chart Vle.

Source: ADA 2015 Consolidated Financial Statements

If the ADA were to commit to a deeper focus on type 1 diabetes the impact could be profound. The organization has an outstanding fundraising infrastructure, strong ties on Capitol Hill, and access to researchers throughout the world. A realignment to type 1 would undoubtedly help increase focus and could ultimately accelerate a cure.
NIH:

Since 1998, the US government has set aside a special budget for type 1 diabetes. The program is managed by NIH in partnership with the Centers for Disease Control and Prevention (CDC) and the US Department of Health and Human Services. Throughout most of the past decade, the annual budget has been set at roughly $150 million. See Chart VIg.

Chart VIg:
NIH Special Diabetes Program Funding: ($ Millions)

Since the program’s inception in 1998, $2.4 billion dollars sourced from taxpayers has been used for type 1 diabetes. In June of 2016, program managers released a report on progress and impact. Overall highlights are shared below, but it is important to note that very little of this investment has been used to advance a Practical Cure.

Highlights:

- The program predominately funds large, multi-center projects, studies, and networks.
- Technology advances, such as the artificial pancreas and improved CGM devices, receive special attention.
- There appears to be some importance attached to bringing solutions to market in the near term, but it does not appear to be a driving factor.
- Major areas of progress:
  - Blood Sugar Control Devices: Significant advances in the artificial pancreas, insulin pumps, and CGM. AP is identified as being on a “fast track” to FDA approval.
  - Beta Cell Replacement: Advances in capability for large-scale laboratory production of functioning beta cells have been achieved - not yet testing in humans.
  - Gene Identification: 50 different genes associated with risk of developing T1D are known, of which 47 were identified after 2013.
  - Eye Disease Complications: There have been significant advances in new therapies.

- There are no active human trials funded by the NIH which support a Practical Cure.
VII. Fundraising for T1D

The ADA and JDRF are the two largest fundraisers for diabetes in the world. Each organization has built an extremely effective fundraising apparatus, combining professional staff with highly passionate volunteers. Both utilize campaigns that are directed nationally but executed on a local chapter level in cities throughout the United States.

Combined, the two organizations hosted 382 national fundraising events in 2016, including walks, rides, and galas. These events generated nearly $350 million in donations, accounting for a significant portion of the annual revenue of the ADA and JDRF.

Most of these nationally-directed events either explicitly or implicitly communicate the proceeds will be used for cure research. Many familiar event names feature a cure message, including JDRF One Walk for a World Without Type 1 Diabetes, Ride to Cure Diabetes, Team JDRF to Cure Diabetes, Tour de Cure, and Step out Walk to Stop Diabetes.

The JDCA has reviewed advertising messages used by the ADA and JDRF at national fundraising events for the last five years. In 2016, 95% of all JDRF national fundraising events featured a cure message, a number consistent with prior years. Yet, only 7% of JDRF’s annual income was utilized for cure research. The ADA featured a cure message in 86% of its 2016 events, but only an estimated 3% of annual income was used for T1D cure research. See Chart VIIa.

In summary, the fundraising promise remains unaligned with the way proceeds are used. As illustrated in Section II of this report, T1D donors clearly prioritize cure research, but only a small proportion of donations are actually used to fund cure research.

“...95% of all JDRF national fundraising events featured a cure message... yet only 7% of JDRF's annual income was utilized for cure research.”

Chart VIIa: 2016 National Fundraising Compared to Actual Allocation

Source: JDCA Proprietary Survey of Donor Sentiment
When making an individual donation, the 4S’s of Good Giving donation guidelines provide a powerful, straightforward, and easy-to-implement approach that will help to ensure that donor generosity is used the way it was intended. See Chart VIIa.

**The 4S’s of Good Giving:**

**Strategy:**

*What are my goals and objectives for giving?*

The only way for donors to be certain that their money is used to achieve the intended impact is to clearly define their goals. A T1D donor that prioritizes cure research, which the majority do as indicated by JDCA surveys, should clarify and establish a goal of influencing cure research, as opposed to anything else.

**Select:**

*Given what I want to achieve, who is the best recipient of my gift?*

There are a multitude of organizations which T1D donors can choose as recipients for their donations. The key for T1D donors is to select an organization which is doing the work that meets their objectives.

T1D organizations can be broken down into three basic groups:

1. Major charities such as JDRF and the ADA
2. Medical research centers, either with a national presence or in your local area
3. Specific research projects

**Specify:**

*When I make my donation, how do I ensure that it is used to achieve my objective?*

This step is the one most often overlooked, but is perhaps the most important. Most charitable organizations prefer to receive funds without restrictions and actively discourage specific gifts so they can use the money for whatever purpose they choose. However, when giving to a charity, the only way donors can ensure the money is used the way they intend for it to be used is to specify.

If you are a donor, the JDCA suggests writing a letter along with your gift specifically stating how the donation should be used. For example: “This donation in the amount of $___ is to be fully used to fund cure research grants.” If the recipient is not willing to use the money to fund cure research they are obligated to return it.

**Substantiate:**

*Was my gift used the way I wanted it to be used?*

Every donor, large or small, has the right to ask how a previous donation was used. This information can help determine whether donors want to continue or alter their giving strategy. Asking how gifts are used also keeps the recipients on their toes and reminds them they are accountable to you, the donor.