PATIENT POWERED RESEARCH

By embracing the reality of data-driven, precision medicine and, thus, radically changing the paradigm of celiac disease research, patients who join *iCureCeliac*® will empower effective treatments and a cure.

INTRODUCTION: CAN WE CURE CELIAC DISEASE? YES, WE CAN.

To cure celiac disease, however, we must fundamentally shift how celiac disease research is conceptualized and conducted. Why? Because the current research paradigm for celiac disease, one that has existed for four decades, has not delivered a cure. Not only has it not delivered a cure, celiac disease research has produced only a single approved treatment for the disease – the gluten-free diet.

The reasons behind the failure of celiac disease research to produce additional treatments supplemental to the gluten-free diet, and a cure are complicated. Celiac disease was once marginalized by the medical community as a rare childhood disorder. As a result, over the last several decades, celiac disease researchers have been denied the adequate resources needed to understand the basic biochemistry of the disease, much less cure it. Thankfully, these researchers soldiered on, despite the hardship, and have learned a great deal. We have learned that:

- celiac disease is a serious autoimmune disease with widespread, systemic manifestations.
- men are as likely as women to contract the disease.
- celiac disease is one of the most common hereditary disorders worldwide.
- celiac disease is associated with a host of serious comorbidities, some of which are fatal.
- a significant number of celiac disease patients suffer from persistent symptoms despite a long-term gluten-free diet.

So, given that we now understand that celiac disease is anything but a "minor" disease, why are there still no FDA-approved treatments or a cure? The short answer is the same as it has always been: money.

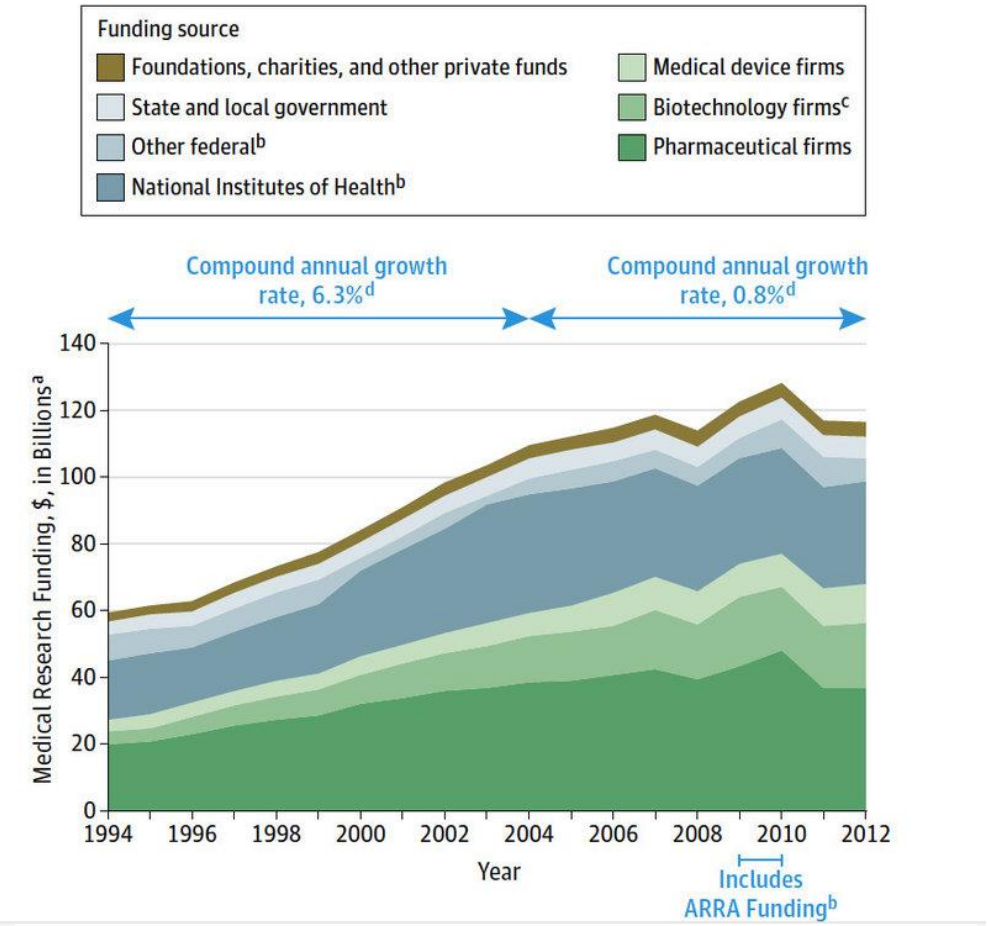
Drug development is incredibly expensive. The Tufts Center for the Study of Drug Development estimates that the cost to *successfully* bring a new drug to market is $2.6 billion, of which $1.4 billion is the average out-of-pocket expense. In 2015, the FDA approved 45 new drugs, significantly higher than the 25 new drugs approved on average between 2005 and 2013.

To understand where celiac disease treatments fit into this model, it is critical to become familiar with the U.S. drug funding model. The vast majority of U.S. biomedical research funding originates from two principal sources. One source is federal agencies, principally the National Institutes of Health (NIH). In 2015, federal funding for celiac disease research was so inconsequential that it did not warrant a line item on the NIH's 200-item long *Estimates of*

Funding for Various Research, Conditions, and Disease list. Highlighted below are other conditions and diseases that begin with the letter '*C'* that made the cut in 2015:

- Charcot-Marie-Tooth Disease $14,000,000
- Chronic Fatigue Syndrome (ME/CFS) $6,000,000
- Cooley's Anemia $15,000,000
- Crohn's Disease $66,000,000

We would never presume to argue that these diseases are not worthy of sufficient funding to warrant a line item on NIH's list. Our argument is that celiac disease is worthy, too.



American Medical Association

U.S. funding for medical research by source, 1994-2012. (Data adjusted to 2012 dollars using the Biomedical Research and Development Price Index.)

While federal funding is vital, nearly 60% of all biomedical research funds comes from the private sector, primarily the pharmaceutical, biotech, and medical device industries.75% of funding for clinical trials, the essential step required to secure FDA approval for drugs and devices, comes from pharma, biotech, and medical device industries.

Because the primary treatment for celiac disease is a strict gluten-free diet, the private sector has not been able to project the return on investment (ROI) needed to convince their shareholders to pour the hundreds of millions of dollars needed into celiac disease research to produce a treatment or a cure. This reluctance continues despite the fact that a significant number of celiac disease patients suffer from persistent symptoms despite a long-term gluten-free diet, and that celiac disease patients live in constant fear of accidental exposure to gluten, which can result in painful symptoms and extended absences from work and school.

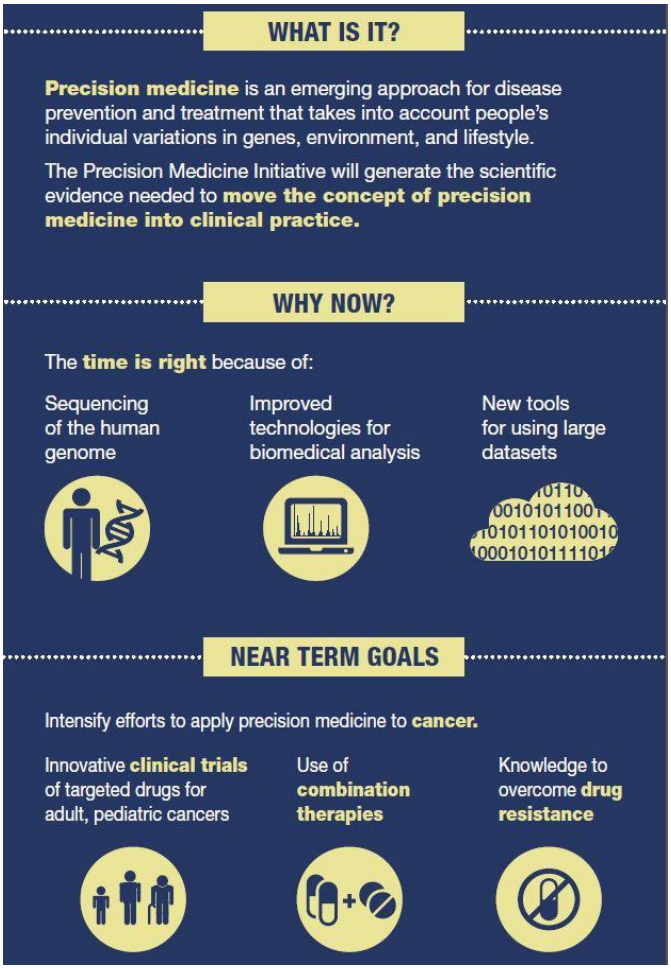
This lack of investment by the feds and pharma into celiac disease treatments and a cure has a devastating and almost hidden side effect. The diagnosis rate for celiac disease is only one in five**.** Millions of Americans are suffering needlessly from a variety of symptoms, including infertility, neuropathy, depression and anxiety, and gastrointestinal disorders. Pharmaceutical sales representatives play a powerful role in continuing disease education for physicians. Because there are no approved drugs or treatments, pharma reps are not educating primary care physicians in their offices, on grand rounds, and at conferences about celiac disease and, thus, not pushing disease awareness. As a consequence, physicians are less likely to recognize the symptoms of celiac disease, understand its familial risk, and to order the simple and inexpensive blood test to screen for it.

CHANGING THE ROI PARADIGM FOR CELIAC DISEASE RESEARCH

Dr. Richard Padzur, head of the FDA's Office of Oncology Products, recently summarized the entire state of the biomedical research enterprise when he said, "As with everything in drug development, it is about reduction of risk."

For decades, Celiac Disease Foundation (CDF) has understood the ROI trap that has strangled celiac disease research. Unlike larger advocacy organizations working on diseases like cancer, Alzheimer's, or Parkinson's, we have never had the financial resources to make the type of investments necessary to catalyze medical research. We have tried to be strategic with our limited resources. For example, CDF invested heavily in advocacy over the last decade to raise the profile of celiac disease in Washington, D.C. An important result of our advocacy work was

the gluten-free labeling law and NIH recognition of celiac disease as a common genetic disorder, affecting both adults and children. Another was influencing the FDA to host its first conference on celiac disease. We have also made targeted investments to improve diagnostic rates and treatment protocols, especially for young adults struggling with the psychological impact of living with celiac disease. None of these projects are changing the ROI paradigm of celiac disease research.



An emerging approach that is shifting the paradigm of biomedical research and drug discovery is precision medicine. Thanks to advances in genomics and big data analytics, disease therapy is moving from developing broad treatments for millions with varying levels of impact, to precise treatments for small groups or individuals with a largely predictable impact. Despite what you might see on television or hear from politicians, we aren't there yet. But we are moving rapidly in that direction. Precision medicine is when researchers use Big Data analytic tools to look at disease and symptom patterns across massive datasets of patients, and then drill down to identify the causes (genetic, environmental, etc.) of the disease or symptoms.

Here is an example. Let's postulate that two family members have the same genetic markers for a disease, yet one actually has the disease and the other does not. Biomedical researchers will want to closely compare the two individuals at every possible level of inquiry, seeking to either isolate what blocked the disease in the healthy patient, or what triggered the disease in the sick patient. In both cases, the researcher will want to replicate those distinguishing factors, and then treat the diseased patient as well as others with the same causality to effect a cure or, at a minimum, an improvement in quality of life. Or, it may lead to a

vaccine or changes in lifestyle or environment to prevent this particular disease. In either scenario, the researcher will know exactly what factor(s), be they genetic, environmental, nutritional, hormonal, etc., to target for treatment. They will also know exactly *whom* to target when it comes to testing the proposed solution in clinical trials. In both cases, knowing what to target with treatment and knowing whom to target to test the efficacy and safety of the treatment is exponentially more efficient than the current method of testing broad-based therapies against largely undifferentiated audiences.

The cost of conducting biomedical research should drop dramatically from the current model as successes and failures come much faster and against smaller data pools. This is the promise of precision medicine.

The data analysis tools used for biomedical research are agnostic: the same algorithms that work to analyze cancer (as in the chart above) or Alzheimer's will work for celiac disease. Additionally, celiac disease researchers are eager to get to work using precision medicine to develop treatments and a cure. What they lack is the massive dataset of patients and their families that powers the kind of analysis that reveals the information that can yield treatments and a cure, and that can feed precise clinical trials to test treatments and a cure.

To spur this lower cost, ROI trap-busting paradigm, CDF was invited by the Genetic Alliance, the University of California, San Francisco, and the University of California Davis, along with nine other disease advocacy organizations, to participate in building a massive, patient-powered database, supported by a grant from the Patient Centered Outcomes Research Institute. As a result, CDF launched its patient registry, iCureCeliac®, on a shared technology and highly secure platform called PEER (Platform for Engaging Everyone Responsibly). iCureCeliac® allows patients to safely contribute medical information and their experiences living with celiac disease and gluten sensitivity online to help researchers improve treatments and find a cure. iCureCeliac® is our key investment that will change the research paradigm for celiac disease.

iCureCeliac® **will lead to life-changing treatments and a cure for celiac disease.**

Since our launch, nearly 2,000 members of our community have added their data to iCureCeliac®. While we are pleased with our launch and the growing embrace of iCureCeliac®, as well as the entire concept of patient-powered cures, we know that we have more to do if we are going to fully effect a change in the celiac disease research paradigm.

Our primary goal is to grow the iCureCeliac® patient registry. For researchers seeking to identify and isolate disease variants and potential treatments and cures, the size of the dataset is critically important. Right now, a research biopharma is preparing to enter phase 2 clinical trials of a drug to treat refractory celiac disease, the rare form of the disease that continues to damage the intestinal villi even when gluten is removed from the diet. Refractory celiac disease also has numerous and even fatal comorbidities, including ulcerative jejunitis, and enteropathy-associated T-cell lymphoma (EATL). This biopharma has begun using iCureCeliac® data to identify targets for the phase 2 trial. Because only 1.5% of all celiac disease patients have refractory celiac disease, the larger the database, the more likely the researchers are to identify both the quantity and quality of patients they need to successfully stage the trial.

Our strategy to grow the database is relatively straightforward. To date, we have focused our efforts on reaching and converting individuals already in our community through our website (celiac.org/icureceliac), via email, and on social media. We must, however, do more.

To be successful, we must reach out beyond our community to the millions of other individuals affected by celiac disease and share our case for joining iCureCeliac® and empowering patient-powered cures. To that end, we have designed a multichannel strategy. **The largest investment we are proposing focuses on identifying potential leads through social/digital media channels**, primarily Facebook and Google networks, and feeding those leads into a conversion campaign to encourage impacted individuals and their families to join iCureCeliac®.

Why are we targeting social/digital media?

1. It is efficient. Facebook has 165 million users in the U.S. who, in 2014, spent an average of 40 minutes a day on the network. Google has 79% of all the searches originating in the U.S. The Taboola display advertising network reaches 87% of all U.S. internet users. The targeting tools available through these digital media networks are incredibly powerful. CDF can put ads into sites of individuals who have searched for celiac disease, gluten-free foods, abdominal bloating, diarrhea, and more. We can use social/digital media buys

to target individuals who have visited celiac.org but who didn't visit our iCureCeliac® page, or individuals who visited the iCureCeliac® page but didn't sign up. We can offer reminders to become part of the cure. Because we can pay principally for those who click through, our investment is much more efficient.

2. We can create and place targeted collateral. Because the media buys are relatively inexpensive to reach the targeted audience, we can invest more into developing great advertising collateral to tell our story of patient-powered cures. We will need to create video, animation, gifs, and effective banners that explain how your participation in a patient registry can lead to a cure and/or treatments for you or a loved one.

This is, by no means, an easy sell.

The decision to share medical history is a deeply personal one. We know that many people are uncomfortable sharing their personal information online and that we need to assure participants that iCureCeliac® is a secure platform addresses their cybersecurity and privacy concerns comprehensively if we are going to get the numbers of participants researchers need.

For this project, we will create a robust iCureCeliac® Conversion Team. Again, through paid and free social media, we will reach out to potential participants to explain to them the concept of building patient registries to empower a cure and to encourage them to join. Next, we intend to recruit and train a group of volunteers who can serve as a support center for potential participants with questions and to help complete their registrations. This personal support includes reassuring participants that their data is both vital and secure, and to explain to participants the iCureCeliac® privacy and access settings and empower them to select access controls consistent with their comfort levels.

We will continue the momentum we have already begun with this major outreach and marketing effort, to build iCureCeliac® into the database that will revolutionize celiac disease research – the database that will lead to a cure.