Welcome

Martha Brumfield, President & CEO

November 7, 2016
Objectives

- Introduce goals of qualifying with regulatory authorities islet autoimmune markers in T1D
- Provide information on C-Path and how the consortium model works
- Provide information about the qualification process
- Achieve consensus on a path forward and garner interest in participating in this effort
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter(s)</th>
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<tbody>
<tr>
<td>11:30 AM</td>
<td>Registration and Lunch</td>
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<tr>
<td>12:00 PM</td>
<td>Welcome and Introductions</td>
<td>Martha Brumfield, C-Path</td>
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<tr>
<td></td>
<td>• Meeting objectives</td>
<td>Jessica Dunne, JDRF</td>
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<td>• Initial Project Proposal</td>
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<tr>
<td>12:45 PM</td>
<td>C-Path Overview</td>
<td>Martha Brumfield, C-Path</td>
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<td>• Q &amp; A</td>
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<tr>
<td>1:15 PM</td>
<td>FDA Perspective on Biomarker Qualification</td>
<td>Dr. Shashi Amur, FDA</td>
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<td>• Q &amp; A</td>
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<tr>
<td>2:30 PM</td>
<td>BREAK</td>
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<tr>
<td>2:45 PM</td>
<td>Consortium Formation/ Structure</td>
<td>Steve Broadbent, C-Path</td>
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<td>• Q &amp; A</td>
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<tr>
<td>3:15 PM</td>
<td>Investigator Perspective</td>
<td>Dr. Åke Lernmark, Lund University</td>
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<td>• Q &amp; A</td>
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<td>4:00 PM</td>
<td>Open Discussion</td>
<td>Steve Broadbent, C-Path</td>
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<tr>
<td>4:45 PM</td>
<td>Summary and Next Steps</td>
<td>Steve Broadbent, C-Path</td>
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<td>• Call to Action</td>
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<tr>
<td>5:00 PM</td>
<td>Adjourn</td>
<td>Martha Brumfield, C-Path</td>
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Qualification of Autoantibodies for T1D

Jessica Dunne, Ph.D.
JDRF
November 7, 2016
Projected Number of Youth < 20 Years With T1D: Increased Incidence Scenario

- Number of US youth with T1D projected to increase 3.3-fold by 2050
- Highest among NHW youth (7.04/1000 in 2050)
- Largest relative increase among Hispanic youth (6.6-fold increase)
- US health care systems need to be prepared

Scientific Framework of Staging of T1D

- T1D is a disease continuum that begins prior to symptomatic disease
- Risk of developing T1D can be identified and quantified
- T1D has well-defined, reproducible early stages that reach a point of inevitability for symptomatic T1D
- Relative rate of progression to symptomatic T1D can be predicted with appreciable accuracy
- The ability to screen for risk and stage T1D prior to symptomatic T1D provides a unique opportunity to delay, and ultimately prevent, symptomatic T1D
Why Change the T1D Diagnostic Criteria?

- Current benefits of risk detection
  - Decreased risk of DKA and hospitalization at diagnosis
  - Greater levels of residual functional beta cell mass at time of initiation of insulin replacement may lead to long-term benefit
- Provides a framework to inform benefit/risk evaluation for regulatory, reimbursement, and clinical care
- Improve the design of prevention trials
- Catalyze risk screening and increase enrollment in natural history and prevention clinical trials
Early Stages of Type 1 Diabetes

Stage 1: Beta Cell Autoimmunity+/Dysglycemia−/ Presymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Beta Cell Autoimmunity+/Dysglycemia+/ Presymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Islet Autoantibodies in T1D

1\textsuperscript{st} generation assays

2\textsuperscript{nd} generation (RIA, ELISA)

- ICA
- Insulin autoantibodies
- ZnT8A
- IA-2A
- GADA
- mIAA
Progression to Symptomatic Stage 3 Type 1 Diabetes from Time of Islet Autoantibody Seroconversion in Stage 1 At-Risk Children with Multiple Islet Autoantibodies

**Total Cohort**

**No. of events**
- No. at risk: 585
- Diabetes: 236
- Lost to follow-up: 92

**Follow-up from seroconversion (years):**
- 0: 585
- 5: 257
- 10: 70
- 15: 8
- 20: 8

**No. at risk**
- Colorado: 69
- Finland: 399
- Germany: 117
- Follow-up from seroconversion (years):
  - 0: 69
  - 5: 38
  - 10: 8
  - 15: 3
  - 20: 5

**Stratified by study site**

**No. at risk**
- Florida: 158
- Germany: 20
- Lost to follow-up: 15

**Follow-up from seroconversion (years):**
- 0: 158
- 5: 41
- 10: 41
- 15: 3
- 20: 5

*JAMA.* 2013;309(23):2473-2479
Probability of Progression to Stage 3 Symptomatic T1D Stratified for Number of Islet Autoantibodies from Birth

![Graph showing the probability of progression to Stage 3 Symptomatic T1D stratified for number of islet autoantibodies from birth.](image)

*JAMA.* 2013;309(23):2473-2479
5- and 10-Year Risk of Progression to Symptomatic T1D with Multiple Islet Autoantibodies ≤ Age 5 Years is 51% and 75%

George Eisenbarth “The clock to T1D has started when islet antibodies are first detected”. Paradigm shift for staging of type 1 diabetes before clinical onset

JAMA. 2013;309(23):2473-2479
Progression to Diabetes in Children with Confirmed Autoantibodies

Asymptomatic type 1 diabetes (%)

P-Value < 0.001 (Log Rank Test)

Years sine first Ab

Number at Risk:

<table>
<thead>
<tr>
<th>Years sine first Ab</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>225</td>
</tr>
<tr>
<td>2</td>
<td>189</td>
</tr>
<tr>
<td>3</td>
<td>146</td>
</tr>
<tr>
<td>4</td>
<td>107</td>
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<td>5</td>
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<td>7</td>
<td>19</td>
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<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Ab+

2 Ab+

3 Ab+

Andrea K. Steck et al. Dia Care 2015;38:808-813
Early Islet Autoantibody Seroconversion Incidence Peak

TEDDY
(Finland, Sweden, Germany, USA)

TEDDY study, 2015
### What About AAb Reversion?

<table>
<thead>
<tr>
<th>Max number of persistent AAbs during follow-up</th>
<th>Total N</th>
<th>AAb reversion pattern during follow-up</th>
<th>N (% of total)</th>
<th>Developed T1D (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single (1 AAb)</td>
<td>225</td>
<td>Reverted</td>
<td>99 (44%)</td>
<td>1</td>
</tr>
<tr>
<td>Multiple (2 AAbs)</td>
<td>161</td>
<td>Reverted 2 AAbs</td>
<td>4 (2.5%)</td>
<td>2</td>
</tr>
<tr>
<td>Multiple (3 AAbs)</td>
<td>210</td>
<td>Reverted 3 AAbs</td>
<td>1 (0.5%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Vehik et al., *Diabetes Care* 2016;39:9:1535-42
AAb Reversion and Disease Progression

Vehik et al., *Diabetes Care* 2016;39:9:1535-42
Early Stages of Type 1 Diabetes

Stage 1: Beta Cell Autoimmunity+/Dysglycemia−/ Presymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Beta Cell Autoimmunity+/Dysglycemia+/ Presymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Metabolic Markers of Symptomatic Diabetes Risk in Multiple Antibody Positive, First Degree Relatives

Abnormal Oral Glucose Tolerance Test

5-Year Risk: 75-80%
Prevalence: 0.7%

*Data includes both children and adults

*Diabetes Care 2005;28:1068–1076
# Early Stages of Type 1 Diabetes: Diagnostic Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage #1</th>
<th>Stage #2</th>
<th>Stage #3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autoimmunity + Dysglycemia – Asymptomatic</td>
<td>Autoimmunity + Dysglycemia + Asymptomatic</td>
<td>New Onset Symptomatic T1D</td>
</tr>
<tr>
<td>Diagnostic Criteria</td>
<td>▪ Multiple AutoAbs</td>
<td>▪ Multiple AutoAbs</td>
<td>▪ Clinical Symptoms</td>
</tr>
<tr>
<td></td>
<td>▪ No impaired glucose tolerance or impaired fasting glucose</td>
<td>▪ Dysglycemia: Impaired Glucose Tolerance and/or Impaired Fasting Glucose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• FPG &gt;100 mg/dL</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• OGTT: 2h PG ≥140mg/dL; 30, 60, 90 min PG ≥200 mg/dL</td>
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<td></td>
<td></td>
<td></td>
<td>• Random plasma glucose ≥200 mg/dL</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• HbA1c ≥5.7%</td>
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<td></td>
<td></td>
<td></td>
<td>• Increasing HbA1c</td>
</tr>
</tbody>
</table>
Why is screening important?

- By getting screened, you may:
  - Enter a prevention trial
  - Avoid hospitalization
  - Help researchers to closely monitor disease progression.

Who is eligible?

- Anyone between the ages of 1 and 45 years with a sibling, child or parent with type 1 diabetes.
- Anyone between the ages of 1 and 20 with a sibling, child, parent, cousin, uncle, aunt, niece, nephew, grandparent or half-sibling with type 1 diabetes.

http://www.pathway2prevention.org/
Stages of Type 1 Diabetes and the Use of AAbs in Clinical Trial Design

Pre-Stage 1: Individuals at-risk for T1D
- General population – 0.4%
- Individuals with high-risk genes – 4%
- First-degree relatives – 3-8%
  - Interventions during pregnancy
  - Interventions at birth/universal interventions
  - Childhood interventions to highest-risk individuals

Stage 1: Beta Cell Autoimmunity/Normoglycemia/Presymptomatic T1D
- Multiple T1D-associated islet autoantibodies with normal glycemic control
  - Oral Insulin Prevention Trial
  - Abatacept Prevention Trial

Stage 2: Beta Cell Autoimmunity/Dysglycemia/Presymptomatic T1D
- Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia
  - Teplizumab Prevention Trial

Stage 3: Beta Cell Autoimmunity/Dysglycemia/Symptomatic T1D
- Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Multiple beta cell autoantibodies specific for human insulin, GAD65, IA-2, or three variants (R, W or Q on position 325) of the ZnT8 transporter are a prognostic marker for disease progression in presymptomatic type 1 diabetes (T1D). The beta cell autoantibodies may be used as an enrichment factor for the design of clinical trials and identification of subjects likely to benefit from interventions being developed for delay of the clinical onset or prevention of symptomatic type 1 diabetes.
BACK-UP SLIDES
Estimated Progression to Symptomatic T1D

Risk is persistently around 11% per year

Diabetes incidence per 100 per year

Year of follow-up after seroconversion

Number Diabetes-free

Follow-up (years)

Bonifacio and Ziegler
Probability of Progression in Islet Autoantibody Positive Relatives of Individuals with T1D Stratified for Number of Autoantibodies (DPT-1)

*Data includes both children and adults

*Data includes both children and adults

*Diabetes Care 2009;32:2269–2274
Progression to Diabetes in Children Expressing One, Two, or Three Autoantibodies by Family History.

[Graph showing progression of asymptomatic type 1 diabetes (%) over years since first antibody detection.]

Andrea K. Steck et al. Dia Care 2015;38:808-813
What About AAb Reversion?

Vehik et al.,
Diabetes Care
2016;39:9:1535-42
5-Year Risk of Progression to Symptomatic T1D in T1D Relatives with Dysglycemia in 75-80% (DPT-1)

Abnormal Oral Glucose Tolerance Test 75-80% 0.7%

*Data includes both children and adults
# Early Stages of Type 1 Diabetes: Potential Clinical Trial Endpoints

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stage #1</th>
<th>Stage #2</th>
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<tbody>
<tr>
<td></td>
<td>Autoimmunity +</td>
<td>Autoimmunity +</td>
</tr>
<tr>
<td></td>
<td>Dysglycemia –</td>
<td>Dysglycemia +</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

### Potential Endpoints of Clinical Trials

- Dysglycemia prevented
- Autoimmunity regulated
- Symptoms delayed, Insulin dependence delayed, prevented
- Dysglycemia reversed
- FPG normalized
- IGT fails to progress to IFG
- HbA1c restored to normal levels; Increasing HbA1c reversed
- Autoimmunity regulated
- Symptoms delayed; Insulin dependence delayed, prevented
Topics

• History of C-Path, What We Do and How We Do It
• What is Qualification?
• What this Consortium Can Do and What It Will Not Do
• C-Path Experience with Data Sharing and Aggregation
• C-Path Track Record
C-Path Mission

The Critical Path Institute is a catalyst in the development of tools to advance medical innovation and regulatory science, accelerating the path to a healthier world. We achieve this by leading teams that share data, knowledge, and expertise, resulting in sound, consensus-based science.
Critical Path Initiative

Independent 501(c)3 founded in 2005 “... to foster development of new evaluation tools to inform medical product development”
C-Path: A Public Private Partnership

• Act as a trusted, neutral third party
• Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  ✓ The best science
  ✓ The broadest experience
  ✓ Active consensus building
  ✓ Shared risk and costs

• Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
• Official regulatory endorsement of novel methodologies and drug development tools
C-Path Consortia

Twelve global consortia collaborating with 1,450+ scientists and 84 organizations

- **Coalition Against Major Diseases**
  Focusing on diseases of the brain

- **Coalition For Accelerating Standards and Therapies**
  Data standards

- **Critical Path for Parkinson’s Consortium**
  Enabling clinical trials in Parkinson’s Disease

- **Critical Path to TB Drug Regimens**
  Accelerating the development of TB drug regimens and diagnostics

- **Duchenne Regulatory Science Consortium**
  Duchenne Muscular Dystrophy

- **International Neonatal Consortium**
  Neonatal clinical trials

- **Multiple Sclerosis Outcome Assessments Consortium**
  Drug Effectiveness in MS

- **Polycystic Kidney Disease Outcomes Consortium**
  New imaging biomarker for PKD

- **Patient-Reported Outcome Consortium**
  Assessing treatment benefit

- **Electronic Patient-Reported Outcome Consortium**
  Electronic capture of treatment benefit

- **Predictive Safety Testing Consortium**
  Drug safety

- **Pediatric Trials Consortium**
  Developing effective therapies for children

**Keywords:**
- Biomarkers
- Clinical trial simulation tools
- Clinical outcome assessment instruments
- Data standards
- In vitro tools
## C-Path Collaborators

### Industry
- AbbVie
- Acorda Therapeutics
- Actelion Pharmaceuticals
- Allergan
- Almac
- Amgen
- AstraZeneca
- Biogen Idec
- Boehringer Ingelheim
- Bracket
- Bristol-Myers Squibb
- Celgene
- Cepheid
- CRF Health
- Daiichi Sanyko
- Edetek
- Eisai
- Eli Lilly and Company
- EMD Serono
- Ephibian
- ERT
- Exco InTouch
- Forest Laboratories, Inc.
- GE Healthcare
- Genentech
- Genzyme
- GlaxoSmithKline
- Hoffmann-La Roche, Inc.
- Horizon Pharma
- ICON
- Ironwood Pharmaceuticals
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Medidata Solutions
- Merck and Co., Inc.
- Meso Scale Discovery
- Millennium: The Takeda Oncology Company
- Mitsubishi Tanabe Pharma Corporation
- Novartis
- Novo Nordisk
- Oracle
- Otsuka Pharmaceutical
- Pfizer
- Pharsight/Certara
- PTC Therapeutics
- PHT
- Sanofi
- Santhera Pharmaceuticals
- Sarepta Therapeutics
- Shire
- Sunovion Pharmaceuticals
- TAG
- Takeda
- Teva Pharmaceuticals
- UCB
- Vertex

### Nonprofit Research Organizations
- Alzheimer’s Association
- Alzheimer’s Drug Discovery Foundation
- Alzheimer’s Research UK
- Bill & Melinda Gates Foundation
- CDISC
- Cincinnati Children’s Hospital
- Engelberg Center for Health Care Reform
- EDCTP
- Flinn Foundation
- Foundation for National Institutes of Health
- National MS Society
- Parent Project Muscular Dystrophy
- Parkinson’s UK
- PKD Foundation
- Reagan-Udall Foundation
- Science Foundation Arizona
- SRI International
- Stop TB Partnership
- TB Alliance
- US Against Alzheimer’s
- CHDI Foundation

### Government and Regulatory Agencies
- Centers for Disease Control and Prevention
- European Medicines Agency
- Innovative Medicines Initiative
- International Genomics Consortium
- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institutes of Health
- National Institute of Neurological Disorders and Stroke
- Pharmaceuticals and Medical Device Agency
- U.S. Food and Drug Administration
- World Health Organization

### Academic Institutions
- The University of Arizona
- Arizona State University
- Baylor University
- University of California San Francisco
- University of Colorado-Denver
- Emory University
- University of Florida
- Johns Hopkins
- Mayo Clinic
- University of Texas Southwestern Medical Center
- Tufts University
C-Path Core Competencies

- Regulatory qualification of preclinical and clinical biomarkers for safety, efficacy, and trial enrichment
- Comprehensive modeling & simulation programs
- Novel in vitro tools to expedite proof-of-concept
- Outcome assessment instrument development
- Clinical data standards development
- Secure data management, standardization, curation, database development
- Forming and managing large international teams as well as collaborative ventures across organizations (e.g., IMI, FNIH)
Biomarker Qualification

• **Definition**: A conclusion that, within a carefully and specifically stated “context of use,” the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development.

• **Context of Use (COU)**: A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development.

• Dr. Shashi Amur (FDA) will cover this in detail.
Biomarker Qualification

• Publicly Announced Decision from FDA regarding acceptance of utility of biomarker within the defined context of use, accompanied by a draft guidance on the use of that/those biomarker(s)

• Publicly Announced Decision from EMA regarding acceptance of utility of biomarker within the defined context of use but without a guidance/guideline

• **VALUE PROPOSITION FOR QUALIFYING BIOMARKERS:**
  - Sponsors of drug development programs have confidence to incorporate biomarkers into their trial designs
  - Regulatory authorities have confidence to rely on biomarkers during their review process
Potential Context of Use Statements for AAbs
Regulatory Qualification

• INITIAL QUALIFICATION GOAL:
  - Multiple beta cell autoantibodies specific for human insulin, GAD65, IA-2, or three variants (R, W or Q on position 325) of the ZnT8 transporter are a prognostic marker for disease progression in presumptomatic type 1 diabetes (T1D).
  - The beta cell autoantibodies may be used as an enrichment factor for the design of clinical trials and identification of subjects likely to benefit from interventions being developed for delay of the clinical onset or prevention of symptomatic type 1 diabetes.

• ULTIMATE GOAL IN THE FUTURE:
  - Prevention of the appearance of one or multiple beta cell autoantibodies specific for human insulin, GAD65, IA-2, and/or ZnT8 can be used as an endpoint in clinical trials as a surrogate marker for prevention of type 1 diabetes.
Consortium Will Focus on Regulatory Qualification

- Letters of Intent to U.S. FDA and to EMA
- Developing Proposed Research Plan to gain necessary evidence
  - Assessing and gaining access to available data on biomarkers
  - Meetings with regulatory authorities
- Executing Research Plan
  - Securing aggregated data set in C-Path data platform
  - Conducting necessary analyses
- Preparing final qualification submission package for regulatory authorities
What We Will Not Do

• **Biomarker discovery** – rather, we focus on biomarker development when a biomarker is close enough to being “regulatory ready”

• **Focus only on writing manuscripts** – rather, we aim for regulatory focused documents to push toward our deliverable to qualify appropriate, evidence-based biomarkers and then we publish accordingly

• **Fund independent research** – rather, we work in a collaborative manner, being good stewards of monetary and in-kind contributions to achieve clearly stated objectives to qualify biomarkers
Key Success Factors for Data Sharing

- Address Range of Objectives for Data Sharing
- Clear Quality Criteria
- Consistent and Transparent Data Process
- Maximize Data Utility Through Standardization
- Ongoing Curation, Validation and Reporting
Data Sharing

- Context of use is key
- Some examples below
- Use cases are not exclusive

<table>
<thead>
<tr>
<th>Use case</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Specific project objective                   | • Biomarker qualification  
|                                              | • Clinical Outcome Assessment qualification  
|                                              | • Disease progression model / trial simulation tools                      |
| Accelerate research in a therapeutic area    | • Research challenges to accelerate discovery (crowdsourcing)            |
| Clinical data transparency                   | • ClinicalStudyDataRequest.com                                           |
Data Capability & Safeguards

Establish a pooled, standardized, secure database of clinical trial data

- **Range of objectives for data sharing drives differences in implementation**
- **Competing requirements need to be addressed**
  - Need to comply with all applicable regulations
  - Need to protect patient privacy (HIPAA and laws in other countries)
  - Need to respect sponsor confidential information and intellectual property
  - Need to optimize utility of shared data
- **Complicated by access and use of data from multiple sources**
- **A wide range of data types need to be handled**
  - Clinical trial data, observational study data, registry data
  - Comprising genotypic, phenotypic, treatment, outcome data
C-Path Data Mapping and Integration Process

Data as contributed

Master Standardized Datasets

Analysis Datasets
PKDOC – FDA Qualification for TKV

“guidance to C-Path’s Polycystic Kidney Disease Outcomes Consortium (PKDOC) for total kidney volume (TKV) as a prognostic biomarker to select patients for clinical trials of new therapies for Autosomal Dominant Polycystic Kidney Disease (ADPKD).”

Dr. Shashi Amur (FDA) will cover this in detail.
Changing the Paradigm for Measuring Disease Progression of PKD

Kidney function (%)

Desired Endpoint

Present Endpoint

Age (years)

0 10 20 30 40 50 60

0 20 40 60 80 100

Courtesy V. Torres
C-Path Consortia have achieved two qualifications by the FDA:

- PKDOC – Imaging of total kidney volume (TKV) as prognostic enrichment factor for clinical trials in polycystic kidney disease.
- PSTC - Final conclusions on the pilot joint European Medicines Agency/U.S. Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers


Fit-For-Purpose accomplishments:

- CAMD - A novel, data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer’s disease

C-Path’s ongoing biomarker qualification programs:

- Drug safety biomarkers for the kidney, liver, pancreas and testes
- Prognostic biomarkers for patient stratification
C-Path Consortia have achieved four qualifications by the EMA:

- **CPTR** - In-vitro hollow fiber system model of tuberculosis (HFS-TB)
- **CAMD** - A novel, data-driven model of disease progression and trial evaluation in mild and moderate Alzheimer’s disease
- **CAMD** - Low hippocampal volume (atrophy) by magnetic-resonance imaging for use in clinical trials for regulatory purpose in predementia stage of Alzheimer’s disease
- **PSTC** - Final conclusions on the pilot joint European Medicines Agency/U.S. Food and Drug Administration VXDS experience on qualification of nephrotoxicity biomarkers
- **PKDOC** – Imaging of total kidney volume (TKV) as prognostic enrichment factor for clinical trials in polycystic kidney disease.

FDA Letters of Support

C-Path consortia have received seven of the eleven Letters of Support issued by the FDA:

<table>
<thead>
<tr>
<th>Requester</th>
<th>Biomarker(s)</th>
<th>Area(s) for Use in Drug Development</th>
<th>Issuance Date with Link to Letter of Support</th>
<th>Requester Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Path, PSTC, Skeletal Muscle Working Group (SMWG)</td>
<td>Serum and Plasma Biomarkers: Myosin Light Chain 3 (My3), Skeletal Muscle Troponin I (sTNI), Fatty Acid Binding Protein 3 (FABP3), Creatine Kinase, Muscle Type (CK-M, the Homodimer CK-MM)</td>
<td>Early Clinical Drug Development</td>
<td>1/22/2015: Letter of Support (PDF)</td>
<td>Refer to Predictive Safety Testing Consortium Web Site</td>
</tr>
<tr>
<td>C-Path, Coalition Against Major Diseases Consortium (CAMD)</td>
<td>Cerebral Spinal Fluid (CSF) Analyte Biomarkers: Aβ1-42, Total tau, Phosphotau</td>
<td>Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer’s Disease Clinical Trials</td>
<td>2/20/2015: Letter of Support (PDF)</td>
<td>Refer to Coalition Against Major Diseases Web Site</td>
</tr>
<tr>
<td>C-Path, CAMD</td>
<td>Magnetic Resonance Imaging Biomarker: Low Baseline Hippocampal Volume</td>
<td>Exploratory Prognostic Biomarkers for Enrichment in Early Stage Alzheimer’s Disease Clinical Trials</td>
<td>3/10/2015: Letter of Support (PDF)</td>
<td>Refer to Coalition Against Major Diseases Web Site</td>
</tr>
<tr>
<td>C-Path, CAMD</td>
<td>Molecular Neuroimaging Biomarker: Dopamine Transporter (DAT)</td>
<td>Exploratory Prognostic Biomarkers for Enrichment in Early Stage Parkinson’s Disease Clinical Trials</td>
<td>3/5/2015: Letter of Support (PDF)</td>
<td>Refer to Coalition Against Major Diseases Web Site</td>
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<tr>
<td>C-Path, Polycystic Kidney Disease (PKD) Outcomes Consortium</td>
<td>MRI, Computed Tomography (CT), or Ultrason (US) Biomarker, Total Kidney Volume (TKV)</td>
<td>Exploratory Prognostic Biomarker for Enrichment in Autosomal Dominant Polycystic Kidney Disease</td>
<td>4/23/2015: Letter of Support (PDF)</td>
<td>Refer to Polycystic Kidney Disease Outcomes Consortium Web Site</td>
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<tr>
<td>The Salle and Faster Evidence-based Translation Consortium (SAFE-T)</td>
<td>Cytokeratin 18 (CK-18), Total and Hyperacetylated High Mobility Group Protein B1 (HMGB1), Osteopontin, and Macrophage Colony-Stimulating Factor 1 Receptor (CSF1R)</td>
<td>Exploratory Monitoring Biomarkers for Use in Drug Development as a Clinical Safety Assessment of the Risk of Drug-induced Liver Injury (DILI) Progression</td>
<td>7/25/2016: Letter of Support (PDF)</td>
<td>Drs. Gerd Kullak-Ublick, Sif Ormandottr, John-Michael Sauer or Douglas Keller or view either the Critical Path Institute Website or the IMI SAFE-T Consortium Website</td>
</tr>
</tbody>
</table>

http://www.fda.gov/drugs/developmentapprovalprocess/ucm434382.htm
EMA Letters of Support

C-Path consortia have received four of the twelve Letters of Support issued by the EMA:

- PSTC – Skeletal Muscle Injury Biomarkers
- PSTC – Translational Drug-Induced Kidney Injury Biomarkers
- PSTC – Translational Drug-Induced Liver Injury Biomarkers
- PD – Clinical Trials Enrichment Tool Using Molecular Imaging of the Dopamine Transporter Biomarker

EMA/FDA Letters of Support

Dual EMA and FDA Letters of Support for DILI (October 2016):

IMI SAFE-T and C-PATH PSTC Obtain Regulatory Support for New Liver Safety Biomarkers

US FDA and EMA Letters of Support Pave the Way for Clinical Qualification

The Innovative Medicines Initiative (IMI) SAFE-T (Safer and Faster Evidence Based Translation) Consortium and Critical Path Institute (C-Path) Predictive Safety Testing Consortium (PSTC) announced today that the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) each issued a Biomarker Letter of Support for new liver safety biomarkers investigated by the SAFE-T Drug-Induced Liver Injury Work Package and the PSTC Hepatotoxicity Working Group. The Drug-Induced Liver Injury Network (DILIN) in the US, an expert network established by The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), contributed their expertise to the research, as well as rare samples from individuals with severe liver injury.
Thank you

www.c-path.org
C-Path Accomplishments

- First preclinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA
- First imaging biomarker for trial enrichment qualified by the EMA (for Alzheimer’s disease)
- First imaging biomarker for trial enrichment qualified by the FDA and EMA (for Polycystic Kidney Disease)
- First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard (Alzheimer’s disease), and additional standards for TB, PD, PKD, MS, and Influenza
- First drug-disease-trial model for AD endorsed by the FDA & EMA
- First Drug Development Tool for TB Qualified by EMA and included in FDA Guidance for TB Drug Development
OVERVIEW

- DDT Qualification
- Biomarkers
- Biomarkers in Drug Development
- Biomarker Development and Qualification
- Role of Consortia in Biomarker Development
- Summary
DDTs are methods, materials, or measures that aid drug development.
DDT QUALIFICATION AT CDER, FDA

Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools


Drug Development Tools (DDT) Qualification Programs Webpage on FDA.gov

“Biomarker,” or “biological marker,” generally refers to a measurable indicator of some biological state or condition.

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

**Types:** Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.

**Examples:**
- Blood glucose (molecular)
- Biopsy-proven acute rejection (histologic)
- Tumor size (radiographic)
- Blood pressure (physiologic)
BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
EXAMPLES OF HOW BIOMARKERS ARE USED IN DRUG DEVELOPMENT

- Mechanism of Action
- Drug Target Selection

- Stratification
- Patient Selection
- Enrichment

- Dose Selection
- Safety Assessment
- Efficacy Assessment

Basic Research

Prototype Design or Discovery

Preclinical Development

Clinical Development

Phase 1

Phase 2

Phase 3

FDA Filing/Approval and Launch

Molecular Pathways Leading to Disease

- Preclinical Safety Assessment
- Mechanism of Action
- Dose Selection
BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT

- Drug Approval Process
- Scientific Community Consensus
- Biomarker Qualification Program
Opportunities
- Focused use
- Data maintained by the biomarker developer

Challenges
- Biomarker data may not be generalizable
- Data aggregation
- Development costs
- Engagement with stakeholder groups
- Biomarker information may be available in drug labels and reviews upon approval
SCIENTIFIC COMMUNITY CONSENSUS APPROACH FOR BIOMARKER DEVELOPMENT

Opportunities
- Knowledge base of exploratory biomarker data in published literature
- Community input

Challenges
- Data reproducibility
- Time to regulatory acceptance
- Variability of study designs, populations, and analytics
- Applicability to regulatory paradigms
ESTABLISHMENT OF ALT AS AN ACCEPTED BIOMARKER FOR REGULATORY USE

- Discovery of Alanine Aminotransferase (ALT)
- Assay Optimization
- U.S. FDA DILI Guidance (Hy’s Law)
- Experimental Optimization
- General Acceptance as a Predictable Drug-Induced Liver Injury (DILI) Biomarker
- Assay Optimization & Standardization

Timeline:
- 1955
- 1978
- 2009
BIOMARKER QUALIFICATION APPROACH FOR BIOMARKER DEVELOPMENT

**Biomarker Qualification Program**

**Opportunities**
- Context of use clearly established
- Pool resources and costs
- Engage outside experts
- Leverage stakeholder groups
- Public guidance with supporting reviews

**Challenges**
- Coordination of stakeholders
- Data may not be widely available
- Data sharing and aggregation
BIOMARKER QUALIFICATION (BQ)

**Definition**: A conclusion that, within a carefully and specifically stated “context of use,” the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development.

**Context of Use (COU)**: A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development.
BIOMARKER QUALIFICATION: SUBMITTER ROADMAP

Stage 1: Initiation
Submit Letter of Intent (LOI)

FDA determines acceptability of LOI

Stage 2: Consultation and Advice
Submit briefing package

Collaborative discussion with FDA regarding the biomarker development plan

Stage 3: Review
Submit full qualification package

FDA reviews package and makes yes/no decision to qualify

FDA drafts guidance document

Publication of Guidance
Draft guidance document posted to Federal Register for public comment

FDA publishes final guidance document
<table>
<thead>
<tr>
<th>General Area</th>
<th>Submitter(s)</th>
<th>Biomarker(s) Qualified for Specific Contexts of Use</th>
<th>Issuance Date with Link to Specific Guidance</th>
<th>Supporting Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonclinical</td>
<td>Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)</td>
<td>Urinary biomarkers: Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil Factor-3</td>
<td>4/14/2008: Drug-Induced Nephrotoxicity Biomarkers</td>
<td>Reviews</td>
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<tr>
<td>Nonclinical</td>
<td>International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group</td>
<td>Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)</td>
<td>9/22/2010: Drug-Induced Nephrotoxicity Biomarkers</td>
<td>Reviews</td>
</tr>
<tr>
<td>Nonclinical</td>
<td>PJ O'Brien, WJ Reagan, MJ York, and MC Jacobsen</td>
<td>Serum/plasma biomarkers: Cardiac Troponins T (cTnT) and I (cTnI)</td>
<td>2/23/2012: Drug-Induced Cardiotoxicity Biomarkers</td>
<td>Reviews</td>
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<tr>
<td>Clinical</td>
<td>Mycoses Study Group</td>
<td>Serum/bronchoalveolar lavage fluid biomarker: Galactomannan</td>
<td>10/24/2014: Patient Selection Biomarker for Enrollment in Invasive Aspergillosis (IA) Clinical Trials</td>
<td>Reviews</td>
</tr>
<tr>
<td>Clinical</td>
<td>Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)</td>
<td>Plasma biomarker: Fibrinogen</td>
<td>7/6/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Chronic Obstruction Pulmonary Disease (COPD)</td>
<td>Reviews</td>
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<tr>
<td>Clinical</td>
<td>Polycystic Kidney Disease Outcomes Consortium</td>
<td>Imaging biomarker: Total Kidney Volume (TKV)</td>
<td>8/17/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Autosomal Dominant Polycystic Kidney Disease</td>
<td>Reviews</td>
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www.fda.gov/biomarkerqualificationprogram
### Biomarker Qualification Program Metrics

<table>
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<tr>
<th>Stage</th>
<th>Number</th>
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<tbody>
<tr>
<td>Number in Initiation Stage</td>
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<tr>
<td>Number in Consultation and Advice Stage</td>
<td>17</td>
</tr>
<tr>
<td>Number in Review Stage</td>
<td>4</td>
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<tr>
<td>Total Number of Active Projects</td>
<td>28</td>
</tr>
<tr>
<td>Number Qualified</td>
<td>6</td>
</tr>
</tbody>
</table>

TYPES OF SUBMISSIONS WE ARE SEEING FOR BIOMARKER QUALIFICATION

19% Patient Selection
26% Preclinical Safety
30% Response
22% Clinical Safety
4% Monitoring

N=27
SOME ENABLERS FOR BIOMARKER DEVELOPMENT

• Data standards
• Data quality
• Data reproducibility
• Statistical considerations
• Assay/imaging considerations/validation
• Assay/imaging protocols
• Establishing cut points
STAKEHOLDERS IN BIOMARKER DEVELOPMENT

Academia

Industry

Biomarker Evaluation/Qualification/Utilization

Regulatory Agencies

Consortia

Federal Partners

Patient Groups, Foundations, and Professional Societies
OPPORTUNITIES FOR ENGAGING FDA IN BIOMARKER DEVELOPMENT
CRITICAL PATH INNOVATION MEETINGS

• Discussion of the science, medicine, and regulatory aspects of innovation in drug development

• Nonbinding meeting

• Not a meeting about a specific approval pathway

• Scope includes early biomarkers and clinical outcome assessments, natural history studies, technologies (not manufacturing), and clinical trial designs and methods

LETTER OF SUPPORT

LETTER OF SUPPORT

• This is a letter issued to a requester that briefly describes CDER’s thoughts on the potential value of a biomarker and encourages further evaluation.

• This letter does not connote qualification of a biomarker. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.


11 letters issued to date
CDER provides an avenue to qualify a biomarker for a “limited” context of use in order to expedite the integration of the biomarker in drug development and to possibly generate additional data that can help in qualifying the biomarker for the “expanded” context of use.
A CONTINUUM, NOT A DICHOTOMY...

Limited and Expanded COU Qualifications:

Qualification Path

- Qualification (1)
- Qualification (2)
- Qualification (3)

Robustness of Context of Use

Expectations:
Data, Evidentiary, and Regulatory

Source: Slide Set from Dr. Martha Brumfield, President and CEO of Critical Path Institute
# Biomarker Qualification Submitters

<table>
<thead>
<tr>
<th>Organization</th>
<th>Number (N=28)</th>
<th>Percentage of Total BQ Submission</th>
</tr>
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<tbody>
<tr>
<td>Consortia</td>
<td>19</td>
<td>68%</td>
</tr>
<tr>
<td>Diagnostics and Biotechnology</td>
<td>4</td>
<td>14%</td>
</tr>
<tr>
<td>Academia</td>
<td>3</td>
<td>11%</td>
</tr>
<tr>
<td>Contract research organizations</td>
<td>2</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Consortium**: A group that is “formed to undertake an enterprise beyond the resources of any one member” (includes disease foundations)

**Contract research organization (CRO)**: is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.
Consortia-pedia is:

- a quantitative and qualitative analysis of the emerging model of collaboration-by-consortium,
- a framework for understanding the breadth and scope of approaches that a wide range of consortia have adopted in efforts to bring together non-traditional partners with a shared R&D goal, and
- designed for stakeholders in medical R&D that are part of a consortium or interested in participating in or creating a consortium.
Consortia products

Products created by consortia

http://consortiapedia.fastercures.org/
Consortia Provide

- A neutral environment to use collective expertise
- Opportunities to pool resources and share costs
- A governance structure for coordination of scientific research to develop biomarkers, leveraging resources and expertise
- Opportunities to bring in outside experts from industry/academia
- Opportunities to have a scientific liaison from government agencies such as FDA and NIH
Summary

• **BEST** (Biomarkers, Endpoints, and other Tools Resource) provides biomarker-relevant definitions, in an effort to harmonize biomarker terminology

• **Biomarker Qualification**
  o Submitter can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance
  o No fees for submissions to the BQ program
  o Biomarker qualification is voluntary
  o Once qualified for a specific context of use, a biomarker can be used by drug developers for other applications

• **New FDA initiatives**, such as LOS and limited COU qualification, can be utilized as early goal posts in biomarker development

• **Consortia** contribute the majority of submissions for biomarker qualification through coordination of collective expertise and shared resources
ACKNOWLEDGEMENTS

Janet Woodcock
ShaAvhrée Buckman-Garner
Suzie McCune
Chris Leptak
Marianne Noone
Sarmistha Sanyal
Kylie Haskins
Ru Chen
OPPORTUNITIES FOR CDER ENGAGEMENT IN BIOMARKER DEVELOPMENT

Biomarker Discovery
- Issued for a promising biomarker with potential application in drug development, based on research findings

Letter of Support
- Issued for a promising biomarker with potential application in drug development, based on research findings

Qualification For Limited Context of Use
- The qualified biomarker undergoes clinical and statistical validation and a qualification guidance is issued for the limited COU

Qualification For Expanded Context of Use
- The qualified biomarker undergoes clinical and statistical validation and a qualification guidance is issued for the expanded COU

Beyond
- The biomarker may be integrated in a new drug application at CDER
Break

Please return by 2:45 pm
Why Form a Consortium?

• Bring together industry, regulators, academic experts, and key societies/foundations to collaborate in areas of common interest
• Solve challenging problems difficult for one organization to tackle
• Engage FDA and EMA for advice to facilitate regulatory approval of new tools and methods
• Spread costs and risks to advance research in areas of unmet need
• Defined governance structure; scientific and project management leadership support, data acquisition and data platform support
• All leading to meaningful regulatory science deliverables
Membership Legal Agreement

• Initial Scope
• Responsibilities and Expectations of Members
• Governance
• Confidentiality
• Intellectual Property
• Publications and Publicity
• Fees
• Anti-Trust
• Anti-Corruption, Anti-Bribery
• Termination, Liability, Indemnification, etc.
Governance Model

• Executive Leadership Team consisting of C-Path executive director and co-director(s) from founding members

• Coordinating committee with representation for all members makes all significant decisions

• Separate Working Groups created to focus on each deliverable – led by a chair or co-chairs
Typical Governance Structure

- Executive Leadership Team
  - Project Manager
  - Coordinating Committee
    - Co-Chairs
      - Working Group
      - Working Group
      - Working Group
      - Working Group
    - Cross WG Teams
Project Management

- Written Goals and Deliverables
- Project Plan with Schedules
- Clear Tasks with Owners
- Tracking and Communicating
- Budgets and Finance
- Meetings and Workshops
Typical Project Schedule

<table>
<thead>
<tr>
<th>ID</th>
<th>Task Name</th>
<th>Duration</th>
<th>2011</th>
<th>2012</th>
<th>3/20/12</th>
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<tr>
<td>38</td>
<td>Map clinical trial data and load database</td>
<td>522 days</td>
<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
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<td>54</td>
<td>Map Mayo Data</td>
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<td>JFMAM JJA AS</td>
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<tr>
<td>55</td>
<td>Map Emory Data</td>
<td>388 days</td>
<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
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<tr>
<td>56</td>
<td>Map U Colorado Data</td>
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<td>JFMAM JJA AS</td>
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<td>4/30</td>
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<td>58</td>
<td>Upload/Verify Mayo, Emory, Colorado Data</td>
<td>10 days</td>
<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
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<tr>
<td>62</td>
<td>Data Loaded/Verified In the Database</td>
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<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
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<tr>
<td>64</td>
<td>Disease Modeling and Simulation</td>
<td>528 days</td>
<td>JFMAM JJA AS</td>
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<td>71</td>
<td>Initiate Modeling and Analysis Phase</td>
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<td>72</td>
<td>Aim 1: Modeling and Simulations Plan</td>
<td>5 days</td>
<td>JFMAM JJA AS</td>
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<td>73</td>
<td>Aim 2: Briefing Package Review</td>
<td>5 days</td>
<td>JFMAM JJA AS</td>
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<td>Aim 3: Disease Progression Model</td>
<td>29 days</td>
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<td>Aim 4: TKV Expansion and Clinical Outcomes</td>
<td>34 days</td>
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<td>Aim 5: Biomarker Qualification Package</td>
<td>40 days</td>
<td>JFMAM JJA AS</td>
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<td>Disease Modeling Results and Review</td>
<td>10 days</td>
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<td>Update BQS Briefing Package</td>
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<td>92</td>
<td>Submit Updated BQS Briefing Package to FDA</td>
<td>0 days</td>
<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
</tr>
<tr>
<td>93</td>
<td>Conduct initial BQRT review of Briefing Pkg</td>
<td>5 days</td>
<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
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<td>Consultation and Advice Phase activities</td>
<td>100 days</td>
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<td>4/30</td>
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<td>FDA agreement to proceed to Review Phase</td>
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<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
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<tr>
<td>96</td>
<td>Prepare Final Qualification Package</td>
<td>40 days</td>
<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
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<tr>
<td>97</td>
<td>Internal Review of Final Qualification Package</td>
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<td>JFMAM JJA AS</td>
<td>4/30</td>
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<tr>
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<td>Finalize Qualification Package</td>
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<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
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<tr>
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<td>Regulatory/Submission Complete</td>
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<td>JFMAM JJA AS</td>
<td>JFMAM JJA AS</td>
<td>4/30</td>
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</table>
Proposal Scope and Timeline

• Development of a data sharing platform for clinical data
• Complete/Update CDISC therapeutic area standard where gaps exist
• Use data to inform the development of regulatory documents and publications
C-Path Policies for Handling of Clinical Data

Key guiding principles:

• We operate as a responsible steward for the clinical data contributed to, used by C-Path, and shared by C-Path

• Data are shared as allowed by contributor

• We will abide by all applicable regulations that govern the use of clinical data
C-Path Online Data Repository

C-Path Data Project Examples
CAMD - AD Clinical Trial Simulation Tool
CPTR - CDC Clinical Trial Data Sharing
PKD - Biomarker Qualification Project
MSOAC – New Outcome Assessment Instrument for MS
Clinical Data Contributed to C-Path

Subjects

Clinical Data: 86 Studies, 50,147 Subjects
Nonclinical Data: 116 Studies, 6,296 Subjects
ReSeqTB: 3,558 Individual Isolates
Funding Models

Funding potentially provided through multiple sources:

• Philanthropic foundations
• Member organizations
• Other grants
• Combination of one or more of the above

C-Path funding model examples:
Next Steps

• Determine who will participate
• Finalize and sign consortium membership agreements
• Announce and formally launch
• Select leadership and staff working groups
• Begin work –
  • Write regulatory Letter of Intent
  • Locate applicable datasets
Thank you

www.c-path.org
Investigator Perspective

Åke Lernmark
Lund University/CRC
Skåne University Hospital
Malmö  Sweden
Type 1 diabetes – an organ-specific autoimmune disease

- **Etiology**
  - Genetic – HLA DR-DQ-DP
  - Environmental factors
  - Contributing genetic factors

- **Pathogenesis**
  - Prodrome at variable rate
  - Autoantibodies are biomarkers

- **Clinical onset and diagnosis**
  - Replacement therapy - insulin
On the Path to Biomarker Qualification

Cytoplasmic ICA kindly provided by the discoverer Franco Bottazzo
“The long and winding road-1”


- 1975 – 1982: several indications that ICA in one lab was not the same as in another.
“The long and winding road-2”

- JDRF sponsored the first workshop in Monte Carlo, October 31, 1985
  - Cytoplasmic islet cell autoantibodies (ICAs) of 13 coded sera were determined by 26 laboratories.
  - The data indicated the requirement of both method improvement and exchange of reference reagents for interlaboratory comparison.
- Immunology of Diabetes Workshops (IDW) was born.
“The long and winding road-3”

• 2nd workshop (1987, Perth, Australia):

  – Coded sera were distributed to 38 laboratories.
  – By including dilutions of sera it was possible to draw a standard curve for each laboratory and this revealed major variations in shape, slope and intercept.
  – A substantial improvement was obtained using each laboratory's standard curve and converting results to units.

• The approach described improves standardisation and will permit laboratories to identify poor assay performance.

• The JDRF Units were born to express levels in relation to a common standard.
“The long and winding road-4”

- Insulin AutoAntibodies (IAA):

- Serum exchange workshops showed that the radiobinding assay was reliable:

- All ELISA tests were disqualified.

- The idea of a conformational epitope was born.

- IAA is yet to be standardized!!!
“The long and winding road-5”- cloned autoantigens enter the scene.

• It started with an immunoprecipitate in 1982: the **64K protein**:
  – GAD65 – cloned in 1991
  – IA-2 - cloned in 1994
  – ZnT8 – cloned in 2007

• **In vitro transcription translation 1992**
  – Several workshops – IDW killed – Immunology of Diabetes Society (IDS) born in 1995 to organize:
    – **Diabetes Autoantibody Standardization Program (DASP)** sponsored by JDRF and CDC.
“The long and less winding road-6”.


- Companies encouraged – ELISAs fell by the wayside

- **WHO standard**: the standard serum used for ICA JDRF Units was used for GADA and IA-2A.
“The WHO standard”.

- WHO Expert Committee on Biological Standards: preparation 97/550 is still available at the National Institute of Biological Standards and Control (NIBSC) as the reference standard for GADA and IA-2A as well as ICA.

- Islet Autoantibody Standardization Program (IASP) is ongoing.
"The DK standard".

Harmonization of Glutamic Acid Decarboxylase and Islet Antigen-2 Autoantibody Assays for National Institute of Diabetes and Digestive and Kidney Diseases Consortium

Ezio Bonifacio, Liping Yu, Alastair K. Williams, George S. Eisenbarth, Polly J. Bingley, Santica M. Marcovina, Kerstin Adler, Anette G. Ziegler, Patricia W. Mueller, Desmond A. Schatz, Jeffrey P. Krischer, Michael W. Steffes, and Beena Akolkar

J Clin Endocrinol Metab, July 2010, 95(7):3360–3367
CHILDREN WITH TWO OR MORE ISLET AUTOANTIBODIES WILL DEVELOP DIABETES.

Staging autoimmune (type 1) diabetes

Etiology: trigger!

1. environmental factors or
2. gene-environment interactions causing appearance of one or more beta cell autoantibodies:
   GADA, IAA, IA-2A or ZnT8A
INVESTIGATOR PERSPECTIVE

• Screening for primary prevention
  – Subjects at increased genetic risk
    • Induce immune tolerance to (pro)insulin (PrePoint) – HLA selected – DR4-DQ8
    • Induce immune tolerance to GAD65 – DR3-DQ2

• Screening for secondary prevention
  – Subjects with autoantibodies and genetic risk
    • Oral insulin (on-going TrialNet)
    • Induce immune tolerance (IA-2, insulin, GAD65 and ZnT8)
    • Other immunomodulatory and combination therapies
What would be the HLA-DQ genotype to select?

The case for Sweden:

<table>
<thead>
<tr>
<th>DQ genotype</th>
<th>Patients %</th>
<th>Controls %</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/8</td>
<td>28</td>
<td>3.5</td>
<td>10.6</td>
</tr>
<tr>
<td>8/8</td>
<td>11</td>
<td>1.7</td>
<td>7.1</td>
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<td>8/6.4</td>
<td>5</td>
<td>1.2</td>
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<td>9.3</td>
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<td>2/2</td>
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<td>3.1</td>
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<tr>
<td>2/9</td>
<td>1.0</td>
<td>0.5</td>
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<tr>
<td>8/6.3</td>
<td>3.3</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>2/6.4</td>
<td>2.2</td>
<td>1.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

From the Swedish Better Diabetes Diagnosis (BDD) study:

Patients: n= 4000
Controls: n= 2000

Persson, Carlsson et al. Submitted for publication

69.0 16.0
Typing by linked SNPs

**Background:** More than 50 regions of the human genome confer T1D susceptibility.

**Aim:** identify sets of SNP combinations to predict T1D in 4,574 patients and 1,207 controls.

**Results:**
AUC 0.87 in the T1DGC set
AUC 0.84 in the validation set.
HLA plus nine SNPs from the PTPN22, INS, IL2RA, ERBB3, ORMDL3, BACH2, IL27, GLIS3 and RNLS genes better than HLA alone.

Next Generation Sequencing Reveals That HLA-DRB3, -DRB4, and -DRB5 May Be Associated With Islet Autoantibodies and Risk for Childhood Type 1 Diabetes

Diabetes 2016;65:710–718 | DOI: 10.2337/db15-1115

Boxplots of risk scores by controls and cases (left panels) and associated ROC curves (right panels) for subjects in the training set only, validating set only and both training and validating sets.
Conclusion, so far......

- HLA typing at birth (cord blood or PKU) to select 15-20% of newborns may identify almost 80% of subjects at lifetime risk for T1D.

- Primary prevention end-points:
  - IAA — First: HLA DR4-DQ8
    - 1-3 years of age — declining thereafter
  - GADA — First: HLA DR3-DQ2
    - 3 years and older

*Does preventing a child from IAA or GADA also prevent later T1D?*
NEWBORNS

• HLA RISK

• PRIMARY PREVENTION

• QUALIFIED AUTOANTIBODIES AS END-POINT
  
  – ORAL INSULIN – (Pre-POINT is the model)
CHILDREN (2-18 years)

- AUTOANTIBODIES – batched type of screening; capillary samples, DBS

- PREVENT THE APPEARANCE OF 2\textsuperscript{nd}, 3\textsuperscript{rd} OR 4\textsuperscript{th} ISLET AUTOANTIBODY

- PREVENT CLINICAL ONSET OF DIABETES

TREATMENT IN CURRENT RESEARCH EFFORTS.

• PRIMARY PREVENTION
  – Oral insulin (Pre-Point)
  – Oral GAD65 (Planned)
  – Combination therapy – induce tolerance

• SECONDARY PREVENTION
  – Oral insulin (TrialNet TN-07 in 2017)
  – Alum-GAD (Helena Elding Larsson in 2017)
WHAT’S IN IT FOR INVESTIGATORS?

• QUALIFIED BIOMARKERS
  – Enable work with primary health care
  – Enable work with hospital laboratories – especially if methods without radioactivity are used

• QUALIFICATION & ACCREDITION
  – Spark interest from industry to develop and improve assays for autoantibodies
  – Expand autoantibody testing in adult diabetes
  – Begin autoantibody testing of schoolchildren
THANK YOU!
Open Discussion

Q & A
Next Steps

• Determine who will participate

• Finalize and sign consortium membership agreements

• Announce and formally launch

• Select leadership and staff working groups

• Begin work

• Write regulatory Letter of Intent

• Locate applicable datasets
Thank You!

www.c-path.org

November 7, 2016