DEFINED HEALTH CAPABILITIES & EXPERIENCE
Rare Disorders and Advanced Therapeutics

Oct 2018
Experience in Rare Disorders
Defined Health Overview in Rare Disorders

**Leader in the identification and evaluation** of new business opportunities for healthcare licensing and business development executives

**Unique and vast understanding of therapeutic areas**, built from conducting thousands of opportunity assessments throughout our history
Defined Health Qualifications in Rare Disorders

- In recent years, DH has conducted numerous projects focused on specialty and ultra-specialty disease settings (within and outside oncology) for clients approaching niche indications from different vantage points:
  - Large pharma exploring “white space” in underserved patient subsets and rare disorders as an expedited route to market, extension of exclusivity and/or life-cycle management
  - Science-driven biotech prioritizing development indications for a novel drug mechanism
  - Biotech orphan pioneer company considering strategic franchise positioning in light of increasing competitive pressures on smaller, microsegmented markets
  - Non-profit patient advocacy foundation evaluating innovative funding instruments for neglected diseases
- We have also lead client specific product searches for potential in-licensing and acquisition targets for biopharma companies interested in entering or expanding their presence in rare disorders.
DH Provides Scientific/Clinical Due Diligence in Undeveloped Indications and Helps to Navigate Developing Markets

- Ultra-orphan disorders represent attractive opportunities for clinical development based on their well-understood pathologies, straightforward paths of intervention (enzyme replacement), involvement of patient advocacy, accelerated development timelines, and premium pricing.

- While the vast majority of these diseases constitute *undeveloped markets* (low diagnosis rate rates, lack of precedents for new drug approval, minimal or no activity in clinical development pipeline), several of these diseases could be thought to represent *developed markets* because there are already drugs approved and commercialized for the indication; or *developing markets* because, though there are no approved products, there is an active clinical stage pipeline of developmental drug candidates targeting the indication.

- Through hundreds of projects focused on Rare Disorders, DH has developed leverageable domain knowledge in rare disorders:
  - Developed a robust and objective method to understand the opportunity for a rare disease therapeutic based on scientific, clinical and commercial criteria
  - Constructed a genetic disease database to expedite the assessment and prioritization of genetic disorder as therapeutic opportunities
  - Created content and moderated symposia and webinars on topics related to rare the opportunities and challenges in sustaining an orphan disease commercial strategy
Clients Often Seek a Better Understanding of Orphan Regulatory Pathways and Incentives

The Orphan Promise: low cost/short timeline development program, friendly regulatory process, pricing flexibility, minimal commercialization costs and market exclusivity

**Development Pros**
- Potential Fast track, priority review
- Tax credits, fee waivers and vouchers
- Grants
- Advocacy support
- Enthusiastic clinical investigators
- Higher than average clinical success rates

**Commercialization Pros**
- 7-year market exclusivity
- Motivated patients
- Advocacy support
- Pricing flexibility
- Minimal competition
- Targeted sales force
## Our Collective DH/Cello Health Rare Disease Experience

<table>
<thead>
<tr>
<th>1025</th>
<th>RARE DISEASE PROJECTS IN THE LAST 4 YEARS</th>
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<table>
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<tr>
<th>&gt;800</th>
<th>RARE DISEASES EXPLORED</th>
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<table>
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<tr>
<th>&gt;160</th>
<th>IN DEPTH RARE DISEASE COVERAGE SINCE 2011</th>
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<table>
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<tr>
<th>&gt;80</th>
<th>RARE DISEASES COVERED IN LAST 12 MONTHS</th>
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<table>
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<tr>
<th>&gt;40</th>
<th>MARKETS COVERED</th>
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### The Type of Work We Deliver

- Asset identification and evaluation
- Clinical Study support
- Forecasting and valuation
- Landscape analysis and gap analysis
- Digital landscape assessment
- Launch strategy development
- Opportunity assessment
- Organizational capability assessment
- Partnering and BD support

- Patient journey and patient flow analysis
- Physician, payer, patient, caregiver insight mapping
- Portfolio and Platform strategy
- Publication planning
- Social media monitoring
- Scenario development
- Scientific platform development
- Strategic and competitive planning
- Thought leader identification and engagement
Rare Disorders Represent Nearly 1/3 of DH Projects: Non-Malignant Genetic Diseases and Rare Cancers are Common Subjects

5 year Project Count by Indication Size
(2013 to 2017e)

Large Population 68%
Rare Disease 32%

Oncology vs. Non-Onc Project Count by Indication Size
(2013 to 2017e)

Rare Oncology 16%
Large Non-Onc 45%
Rare Non-Onc 16%
Large Oncology 23%

DH Internal Project Data
DH’s Rare Disease Experience Crosses All Therapeutic Areas, Involving Patient Segments with a Wide Degree of Disease Burden

- Half of DH’s projects focus on orphan oncology while the other half on non-malignant disorders scattered across all therapy areas:
  - Each afflict a relatively small population, but combined make up one of the highest value categories
  - Some are idiopathic or acquired disorders, but many are inherited, monogenetic diseases
  - Have a wide degree of severity, age of onset and clinical presentation
  - Represent attractive opportunities for clinical development as a result of their:
    - well understood etiologies & pathologies
    - straightforward paths of intervention (e.g. enzyme replacement, substrate reduction, mRNA knockdown)
    - accelerated development timelines
    - premium pricing models

DH Internal Project Data
DH Assessments of Therapies for Rare Disorders Cross All Platforms

- Assessments in rare disorders typically cross all technologies platforms from traditional small molecule and biologics to complex therapeutics including nucleic acid based oligonucleotide and gene/vector based therapies, viral therapies, cell therapies and drug device combinations

<table>
<thead>
<tr>
<th>Therapeutic Interventions</th>
<th>Small Molecule Modulators</th>
<th>Protein Augmentation</th>
<th>Antibodies</th>
<th>Peptides and Nucleic Acids</th>
<th>Gene Correction &amp; Augmentation</th>
<th>Cell Therapy / Regen Med</th>
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</thead>
<tbody>
<tr>
<td>SMIs</td>
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<td></td>
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<td>Other cell sources: e.g. ES, iPS</td>
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<tr>
<td>Chaperones</td>
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<td>Devices</td>
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<td>Substrate Reduction</td>
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<td></td>
<td>– Encapsulation – Scaffolds – Implants – Micro- organs – Aphaeresis</td>
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<tr>
<td>Transcription / Translation enhancers</td>
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<td>Epigenetics</td>
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</tbody>
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Core Capabilities and Services
Defined Health Core Services

### Opportunity Assessments

- Assess commercial value in markets of interest
- Evaluate mechanistic approach and scientific rationale
- Position and differentiation from evolving SoC
- Define target patient populations, clinical endpoints and target product profiles
- Determine payer perspective

### Portfolio and Platform Strategy

- Analyze and prioritize pipeline portfolio
- Identify and assess novel indications for development
- Prioritize and sequence potential indications
- Define value inflection strategy for clinical candidates
- Advise on optimal time and stage of development for partnering

### Asset Identification and Evaluation

- Establish criteria for identifying programs that fit with strategy
- Evaluate and rank assets and/or companies that best match criteria
- Provide deeper analysis of priority targets across including competitive landscape and differentiation
- Identify value inflection points to optimize partnering strategy
Deep Knowledge Across Therapeutic Areas

- Defined Health has a deep knowledge base within and across all therapeutic categories.
- The focus of our work closely mirrors the therapeutic area focus of today’s biopharmaceutical pipeline.
- Defined Health’s research is conducted by its trained consultants, all of whom have PhD or MS degrees and/or significant relevant experience in pharma and the targeted scientific areas.
- Our consultants possess a combination of commercial, scientific, and clinical knowledge that enable comprehensive analyses and actionable recommendations.

And emerging areas of interest such as NASH & fibrosis
Insight Across the Clinical Development Value Chain, with Particular Focus on Early-Stage Assets

Defined Health’s combination of scientific sophistication and strategic/commercial insight provides a competitive advantage for its core offerings across the clinical development value chain, with particular emphasis on assets in early phases of development.
Insight from Key Stakeholders

- Defined Health has developed an extensive network of relationships with key stakeholders.
- Our consultants conduct in-depth collegial discussions with physicians and payers to understand their perspective on the value of development-stage assets as well as product portfolios and platforms.
- We also have the ability to do patient research to gain key insights into patient needs and willingness to pay for new products.
Forecasting and Valuation

- Financial forecast modeling is an essential component of Defined Health’s valuation capabilities. We build revenue forecasts (patient- or prescription-based) in a user-friendly Excel format to allow our clients to see in real-time how changes and sensitivities around distinct variables impact the forecast.

- In addition, we provide benchmarking valuation of individual assets, platforms and company portfolios as well as risk-adjusted NPVs in Excel with sensitivity analysis surrounding the key inputs.

Patient Population & Treatment
- Epidemiology
- Key patient segments based on treatment practices
- Addressable patient segments

Competition
- Current and future competitive landscape
- Impact of new entrants/generics/ biosimilars
- Impact of competition on peak revenue potential

Penetration
- Anticipated use based on product’s value proposition
- Potential adoption & uptake
- Appropriate analogs

Pricing
- Appropriate/acceptable price based on current & future market
- Impact of market access landscape on pricing potential
- Potential level of rebating/discounts
Search & Evaluation of Opportunities

- Defined Health assists clients by helping to define and execute on strategic goals to either establish a new presence or grow an existing presence in specific therapeutic and specialty areas.

- We have established a comprehensive & transparent process for identification and qualification of actionable partnering and in-licensing opportunities against a defined set of criteria to help strengthen the company’s portfolio.
Defined Health’s Rare Disorders and Genetic Disease Database
Defined Health Genetic Disease Database

- Defined Health has created a database of genetic diseases sourced from OrphaNet, National Institutes of Health Genetics Health Reference (NIH GHR), National Organization for Rare Disorders (NORD), Online Mendelian Inheritance in Man (OMIM).
- DH is able to efficiently filter the database based on multiple categories characterizing genetic diseases. This process allows DH to prioritize and identify genetic diseases to enhance the positioning of potential new gene therapies in the competitive landscape.
Methodology: Creation of the DH Genetic Disease Database

- Funnel displays the filtering process Defined Health used to create a working list of verified genetic diseases

1. **STEP 1**
   - Genetic/Rare Disease Database
     - Defined Health’s genetic/rare disease database consists of ~9,500 diseases from multiple rare disease databases including but not limited to: OrphaNet, NIH GHR, NORD

2. **STEP 2**
   - Filtered based on disease etiology
     - Filtered database to remove diseases that do not fit screening criteria (idiopathic, gross chromosomal anomalies, poison/toxicities, etc.).

3. **STEP 3**
   - Filtered based on prevalence
     - Applied automated process to acquire prevalence data from rare disease databases (Orphanet, GHR, NORD) based on disease OMIM codes.

4. **STEP 4**
   - Filtered based on worldwide prevalence
     - Filtered on diseases with "significant" prevalence as defined as >1 in 1,000,000 worldwide.

5. **STEP 5**
   - Relevant genetic diseases
     - Further filtered out diseases that do not fit screening criteria (cancer indications, no clear scientific evidence of genetic cause).

Genetic diseases for further characterization (severity, mutation type, unmet need, etc.)

Sources: DH genetic disease database, OrphaNet, National Institutes of Health Genetics Health Reference (NIH GHR), National Organization for Rare Disorders (NORD), Online Mendelian Inheritance in Man (OMIM)
Below is a representative screenshot of the DH genetic disease database filtered on: monogenic, loss of function mutation type, and liver affecting.

Final output can be further tailored to include additional criteria of interest not already captured.

Source: DH genetic disease database
Example: Therapeutic Area Breakdown of DH Genetic Disease Database

Primary Therapeutic Area Breakout of Genetic Diseases with Significant WW Prevalence

- Approximate breakdown of therapeutic area distribution in the DH genetic disease database
- DH can filter the database on any TA's of interest for deeper investigation
- Additionally, DH can filter on affected organs to further identify potential indications of interest (see following slide)

Sources: DH genetic disease database, OrphaNet, National Institutes of Health Genetics Health Reference (NIH GHR), National Organization for Rare Disorders (NORD), Online Mendelian Inheritance in Man (OMIM)
Information Provided By DH Rare Disease Database

- DH utilizes the secondary the sources on the right to characterize each disease:
  - therapeutic area
  - description/disease manifestation
  - synonyms
  - segmentation
  - genetic transmission
  - gene mutated/cause
  - gene size
  - protein mutated or impacted
  - gene product locations (tissue, intra/extracellular)
  - gene function in normal vs. mutated form
  - type of mutation (loss/gain of function, missense, etc.)
  - diversity of mutations (# of different mutations with key mutations identified, % patients with mutations)
  - epidemiology: prevalence, incidence
  - severity / unmet need
  - age of onset

Selected Data Sources

- NCBI OMIM ClinVar
- HGMD
- GeneTests / Gene Reviews
- National Organization for Rare Disorders [NORD]
- Orphanet
- National Institutes of Health Genetics Health Reference [NIH GHR]
- Clarivate Analytics Cortellis
- ADIS R&D Insight
- EvaluatePharma
- Medical info sites (Medscape, UpToDate)
- Company websites and press releases
- Analyst reports
- Clinical trial databases
- Defined Health’s Knowledgebase
Example of Single Abridged Entry – Hereditary Emphysema

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Hereditary Emphysema (Alpha-1-antitrypsin deficiency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic Area</td>
<td>Respiratory disorders</td>
</tr>
<tr>
<td>Description / Disease manifestation</td>
<td>Alpha-1 antitrypsin deficiency (A1AD) is a hereditary disorder characterized by low levels of a protein called alpha-1 antitrypsin.....</td>
</tr>
<tr>
<td>Synonyms</td>
<td>A1AD, AATD, genetic emphysema</td>
</tr>
<tr>
<td>Genetic Transmission</td>
<td>Autosomal co-dominant genetic condition</td>
</tr>
<tr>
<td>Gene mutated / Cause</td>
<td>SERPINA1 gene</td>
</tr>
<tr>
<td>Protein mutated or impacted</td>
<td>Alpha-1 antitrypsin</td>
</tr>
<tr>
<td>Location of gene expression, Secreted protein?</td>
<td>Secreted</td>
</tr>
<tr>
<td>Gene function in normal vs. diseased (impact on protein expression and biology)</td>
<td>Normally, this protein is produced in the liver and released in the blood and functions to protect.....</td>
</tr>
<tr>
<td>Type of mutation (loss of function, gain of function, missense, etc.)</td>
<td>Loss of function</td>
</tr>
<tr>
<td>Diversity of mutations (# of different mutations with key mutations identified, % patients with mutations)</td>
<td>One gene, over 120 different mutations in the gene identified, with the most common termed S and Z....</td>
</tr>
<tr>
<td>Prevalence</td>
<td>100,000 Americans, with only estimated 10% diagnosed</td>
</tr>
<tr>
<td>Incidence</td>
<td>1/1,500 to 3,500 in those with European ancestry, but overall prevalence unknown</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>Adulthood (20-50)</td>
</tr>
</tbody>
</table>
Example Indication Prioritization Process from Rare Disease Database

Prioritization Criteria

• From a starting list of >1,500 groups of disorders, a more tractable set of indications can be narrowed by applying screening criteria determined by collaboration with client. For example:

  • Severity: High unmet need, poor SOC
  • Scientific Risk: Biologically tractable
  • Market Size: epidemiology, commercial opportunity
  • Platform: specific criteria for therapeutic approach
  • Competition: development pipeline activity
  • Development Risk: Short path to translational POC - Established animal models and therapeutic endpoints
  • Clinical Risk: Established clinical endpoints, approved product
  • Regulatory Risk: Orphan, breakthrough status potential
  • Partnerability: Known pharma interest in disease/target
### Example Evaluation Prioritization Criteria

#### Summary of Relative Rankings For Opportunities Identified as Attractive

<table>
<thead>
<tr>
<th>Criteria</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epi/Market Size</td>
<td>Larger epidemiology and/or Market size: (&gt;2K candidates for gene therapy) AND (Current or e2022 WW market &gt;$500M)</td>
<td>Larger US epi or Market size: (&gt;2K candidates for gene therapy) OR (Current or e2022 WW market &gt;$500M)</td>
<td>Low US epi and Market size: (&lt;2K candidates for gene therapy) AND (Current &amp; e2022 WW market &lt;$500M)</td>
</tr>
<tr>
<td>Unmet Need</td>
<td>High unmet need: No effective and safe therapies for management of indication</td>
<td>Moderate unmet need: Current SoC is somewhat effective</td>
<td>Low unmet need: Current SoC is very effective and safe for management of indication</td>
</tr>
<tr>
<td>Competition</td>
<td>Limited number of gene/cell therapies in clinical or preclinical development: (&lt;5 programs)</td>
<td>Moderate number of gene/cell therapies in clinical or preclinical development: (5-15 programs)</td>
<td>High number of gene/cell therapies in clinical or preclinical development: (&gt;12 programs)</td>
</tr>
<tr>
<td>Biologic/Validation</td>
<td>HSC Transplant is SOC for some or all patients affected by indication</td>
<td>HSC Transplant rarely used in clinic, but there are BMT case reports and/or clinical development of ex vivo therapies requiring conditioning regimen</td>
<td>No use of HSC Transplant or interest in developing ex vivo products requiring conditioning regimen</td>
</tr>
<tr>
<td>ORF Size (bp)</td>
<td>Small ORF size of affected gene: (&lt;1,000 bp)</td>
<td>Moderate ORF size of affected gene: (1,000-6,000 bp)</td>
<td>Large ORF size of affected gene OR multiple genes affected: (&gt;6,000 bp)</td>
</tr>
<tr>
<td>Time to POC Endpoint (Months)</td>
<td>Short post-treatment follow up time, per patient, for readout of efficacy endpoint: (&lt;3 months)</td>
<td>Moderate post-treatment follow up time, per patient, for readout of efficacy endpoint: (3-6 months)</td>
<td>Long post-treatment follow up time, per patient, for readout of efficacy endpoint: (&gt;6 months)</td>
</tr>
<tr>
<td>Time to Approval (Yr.)</td>
<td>Shorter required pivotal trial: (0-3 years)</td>
<td>Moderate required pivotal trial: (3-5 years)</td>
<td>Longer required pivotal trial: (&gt;5 years)</td>
</tr>
<tr>
<td>Approval Trial Size (Pat. #)</td>
<td>Smaller required # of patients: (0-25 patients)</td>
<td>Moderate required # of patients: (25-75 patients)</td>
<td>Larger required # of patients: (&gt;75 patients)</td>
</tr>
</tbody>
</table>
Monogenetic Disorders Have Diverse Etiology Depending on the Location of Expression and Function of a Mutated Gene Product

Monogenetic Neuromuscular Disorders are caused by inherited and sporadic mutations in genes involved in motor unit structural and electrical function, and also metabolic and biochemical physiology providing energy and support for neuromuscular health and functioning.

15 Broad Categories of Inborn Errors of Metabolism

Disorders of amino acid and peptide metabolism
- Disorders of branched-chain amino acids metabolism
- Disorders of phenylalanine metabolism
- Disorders of tyrosine metabolism
- Disorders of tryptophan metabolism
- disorders of urea cycle metabolism

Disorders of fatty acid and ketone body metabolism
- Disorders of medium-chain fatty acid oxidation
- Disorders of very-long-chain fatty acid oxidation
- Disorders of ketone body metabolism
- Disorders of fatty acid oxidation

Disorders of carbohydrate metabolism
- Disorders of fructose and glycogen metabolism
- Disorders of galactose metabolism
- Disorders of glucose metabolism
- Disorders of gluconeogenesis
- Disorders of glycogen deficiency
- Disorders of ketone body metabolism
- Other carbohydrate disorders

Disorders of energy metabolism
- Disorders of fatty acid oxidation
- Disorders of glucose metabolism
- Disorders of glycogen metabolism
- Disorders of ketone body metabolism
- Disorders of long-chain fatty acid oxidation
- Disorders of medium-chain fatty acid oxidation
- Disorders of organic acid metabolism
- Disorders of organic anion transport
- Disorders of organic cation transport
- Disorders of organic anion transport

Disorders of the metabolism of purines, pyrimidines and nucleotides
- Disorders of purine metabolism
- Disorders of pyrimidine metabolism
- Disorders of purine nucleotide metabolism
- Disorders of pyrimidine nucleotide metabolism

Disorders of neurotransmitter metabolism
- Disorders of gamma-aminobutyric acid (GABA) metabolism
- Disorders of thyroid hormone metabolism
- Disorders of tyrosine metabolism
- Disorders of serotonin metabolism
- Disorders of dopamine metabolism
- Disorders of norepinephrine metabolism
- Other disorders of neurotransmitter metabolism

Disorders of the metabolism of steroids and hormones
- Disorders of steroid hormone biosynthesis and metabolism
- Disorders of sex steroid hormone biosynthesis and metabolism
- Disorders of thyroid hormone biosynthesis and metabolism
- Disorders of vitamin D metabolism
- Disorders of vitamin E metabolism
- Disorders of vitamin A metabolism
- Disorders of vitamin B metabolism
- Disorders of vitamin K metabolism
- Disorders of vitamin B metabolism
- Disorders of vitamin C metabolism

Disorders in the metabolism of fatty acids and lipids
- Disorders of fatty acid oxidation
- Disorders of very-long-chain fatty acid oxidation
- Disorders of medium-chain fatty acid oxidation
- Disorders of ketone body metabolism
- Disorders of organic acid metabolism
- Other disorders of organic acid metabolism

Disorders of protein synthesis and function
- Disorders of amino acid metabolism
- Disorders of protein synthesis and function
- Disorders of protein folding and processing
- Disorders of protein targeting and function
- Disorders of protein degradation
- Other disorders of protein function

Disorders of glycosylation and other disorders of protein modification
- Disorders of glycosylation and other disorders of protein modification
- Disorders of protein folding and processing
- Disorders of protein targeting and function
- Disorders of protein degradation
- Other disorders of protein function

Other disorders of organic acid metabolism
- Disorders of organic acid metabolism
- Other disorders of organic acid metabolism

the Study of Inborn Errors of Metabolism
Example Output: Graphic of Clinical Validation vs. Unmet Need
Example Output: Rare Disorder Profile

Market Overview: Cystinosis

Cystinosis is a lysosomal storage disease characterized by the accumulation of cystine in various tissues. Mutations in the CTNS gene, which encodes a transporter for cystine, lead to an inability to excrete cystine. Two main types of cystinosis are described:

- Infantile (neonatal) cystinosis
- juvenile cystinosis

Both types are caused by mutations in the CTNS gene, with infantile cystinosis being the more severe form. Symptoms include renal disease, cataracts, and other organ failures.

Disease Overview: Cystinosis

Overview

- Cystinosis is an autosomal recessive disorder caused by mutations in the CTNS gene.
- The disease is divided into two main types:
  - Infantile (neonatal) cystinosis
  - Juvenile cystinosis
- Infants with cystinosis typically present within the first six months of life with symptoms such as failure to thrive, lethargy, and developmental delay.

Clinical Context: Cystinosis

- Premature death is common in untreated cases of infantile cystinosis.
- Treatment typically involves a combination of medications, dietary modifications, and regular monitoring.

The image contains diagrams and tables that illustrate the disease's progression and treatment. The text provides a detailed overview of the disorder, including its genetic basis, clinical manifestations, and management strategies.
Client Cases in Rare Disorders
Client Cases in Rare Disorders Cross All Therapeutic Areas

- Evaluation of inborn errors of metabolism (IEMs) such as Gaucher, Fabry, Pompe, phenylketonuria (PKU), acidosis and urea cycle disorders
- Prioritization of IEMs for a novel small molecule substrate reduction and chaperone therapeutic
- Repositioned several assets for Familial Hypercholesterolemia (HoFH/HeFH) and other deficiencies of cholesterol metabolism
- Metabolic bone diseases such as alkaline hypophosphatasia and osteopetrosis
- Duchenne Muscular Dystrophy (DMD) and other structural neuromuscular dystrophies
- Assessment of an exon-skipping therapy for Spinal Muscular Atrophy (SMA)
- Landscape assessment of mitochondrial myopathies and evaluation of small molecule modifiers of energy balance and ubiquitylation
- Search and evaluation of gene transfer platforms for neurology indications, prioritization of hundreds of monogenetic disease with CNS involvement
- Evaluation of the future of the Alpha-1-antitrypsin deficiency and hereditary emphysema markets
- Opportunity searches for potential in-licensing and acquisition targets for orphan respiratory diseases, cystic fibrosis, bronchiectasis, pulmonary hypertension and Idiopathic Pulmonary Fibrosis
- Competitive landscape assessment for Prader-Willi Syndrome
Client Cases in Rare Disorders Cross All Therapeutic Areas

- Detailed competitive analysis & forecasting for next generation approaches in myeloproliferative disorders (myelofibrosis, polycythemia vera, essential thrombocytosis), paroxysmal nocturnal hemoglobinuria (PNH), hereditary angioedema (HAE), Diamond Blackfan anemia (DBA), Primary Immune Disorders such as severe combined immunodeficiency (ADA Deficiency, X-SCID), Wiskott-Aldrich Syndrome, etc.

- Review of IgG market and search for next generation innovations including novel approaches (Fc) and improved delivery

- Evaluated acute and chronic therapies for hemoglobinopathies such as sickle cell anemia and thalassemias

- Opportunity assessment in iron overload for heavily transfused thalassemia and sickle cell anemia patients including revenue forecast

- Detailed competitive analysis & recommendations for next generation approaches in blood diseases such as hemophilia, idiopathic thrombocytopenic purpura (ITP), and myelodysplastic syndromes

- Complete review of hemophilia A and B pipeline for competitive landscape and opportunity search, including market overview, unmet needs assessment and alignment of pipeline TPPs with unmet needs [Includes review of inhibitor issues]

- Indication prioritization of novel antiplatelet therapies and anticoagulants

- Evaluation of benign hematology indications to gene edited hematopoietic stem cell (HSC) therapeutics
Client Cases in Rare Disorders Cross All Therapeutic Areas

- Needs assessment of **entire blood cancer space** (14 broad indications and many subsets) for a large non-profit organization
- Numerous assessments of clinical stage products in development for malignant hematology (**AML**, **MDS**, **DLBCL**, **MM**, **CLL**, **iNHL**, **PTCL**, **CTCL**)
- Assessment of the **cord-blood transplant** market for a novel cell expansion technology
- Assessment of **improved IV and oral transplant conditioning cytotoxic agents**
- Technological landscape review of the **adoptive cellular therapy space** (**CART**, **TCR**, **CTL**, **TIL**, **NK**)
- Prioritization of **tumor associated antigens (TAAs)** and contraction of protoproducts for heme and solid tumors
- Prioritization of **~150 rare hematologic malignancies** based on epidemiology, unmet need and natural history for a novel metabolic drug
- Assessment of IL-6 mAb for **Castleman's disease**
- Evaluation of CD19, BCMA and other targets for bispecific antibody T-Cell engaging platform
- Competitive landscape and market forecast for FGFR Ligand Trap in **mesothelioma**
- Opportunity assessment of IO agent in two rare heme malignancies: **eosinophilic leukemia** and **mastocytosis**
- Prioritization of gene editing therapeutics across **genetic diseases** and **oncology**
- Rare disease, ultra-specialty search for commercial biotech company across **non-malignant heme, immunology, respiratory, neurology**
Client Cases in Rare Disorders Cross All Therapeutic Areas

- Prioritization of potential future label indications for a marketed biologic immunotherapeutic among many areas of evidence based medicine in **autoimmune disorders**
- Identification and prioritization of potential **orphan indications** for broad acting mechanism antibodies (several projects) [Identified indications with potential rapid clinical development path with potential to result in earlier commercialization vs. crowded lead indications (e.g. RA and SLE)]
- Early clinical stage asset search across a variety of rare disease areas including **metabolic, gastrointestinal, cardiovascular, endocrinology** and **genitourinary**
- Market assessments for expanded indications of marketed injectable product for **spasticity** and other orphan indications
- Evaluations of movement disorders such as **Parkinson disease** and **Huntington chorea**
- Landscape assessment of the **multiple sclerosis (MS)** market and evaluation of novel therapeutics
- Opportunity assessment for device in development for **retinitis pigmentosa**, focused on identifying subsets of patients with severe blindness, highlighted marketing challenges relating to multidisciplinary patient management, and examined **cochlear implant** market as surrogate
- Opportunity assessment for novel agent in Phase 2 for **Huntington’s disease** and advised on strategic development (Phase 3 endpoints in different aspects of the disease such as cognition and movement) to maximize value to payers and provided relevant value based pricing model to support revenue forecast in multiple scenarios
Rare Disorders Projects Often Involve Advanced Therapies

- Evaluation of mesenchymal cell therapy for myocardial infarction, heart failure and inflammatory disorders for a small biotech
- Prioritization of therapeutic proteins gene transduced cell-based dermal delivery platform that fit technical specifications and meet benchmarks for differentiation for a small biotech
- Benign hematology landscape assessment and identification of gene/cell therapy platforms with development project aligned with patient needs for a large biophama
- Search of NORD and development database to find good targets for gene augmentation therapy platform (i.e. complement loss of function mutations)
- Evaluation and forecast of a cord blood ex vivo expansion technology for allogeneic stem cell transplant
- Search for moderately rare monogenetic diseases caused by defects in secreted proteins that may be addressable with gene therapy
- Opportunity assessment for gene-based therapy for wet age related macular degeneration wet AMD product in phase 2b
- Evaluation of Epo reformulation in micro-organ for neurodegenerative diseases of the eye (glaucoma, retinitis pigmentosa, possibly others) also for traumatic brain injury
- Assessment and forecast of an allogeneic stem cell transplant technology
- Search for distressed companies developing non-viral gene and cell therapy platforms for M&A roll-up opportunities
- Opportunity assessment for a proapoptotic gene therapy for cancer, provided valuation forecast of 5 cancer indications
- Prioritization of oncology, AIID indications, and cell therapy approaches for a CRISPR/Cas9 platform
# Advanced Therapeutics

## Recent Case Study: Analysis of Gene Therapy Landscape

### The Client

- US-based biotech with single asset gene therapy in late-stage development for treatment of debilitating monogenetic disorder
- Planning follow-on development with same agent in analogous disease subtypes

### Business Challenge

- Seeking to broaden its gene therapy portfolio by bringing additional assets into its pipeline
- Considering acquisition of new gene therapy technologies within the context of existing domain expertise

### Our Approach

- Exhaustive analysis of gene therapy landscape including overview of gene transfer systems and various enabling technologies
- Interaction with key personnel at vector cores, research institutes and biotechs in order to assess licensing or M&A opportunity

### Valued Outcome

- Comprehensive searchable database of gene therapy programs in academia and industry
- Facilitate discussion on gene transfer systems, platforms and most tractable indications with client and relevant stakeholders
### Advanced Therapeutics

**Recent Case Study: Identification, Cross-Comparison, and Prioritization of Putative Targets and Associated Indications Aligned With the Value Proposition and Competitive Opportunities to be Pursued With a Differentiated but Early-Stage ACT Platform**

#### Oncology

<table>
<thead>
<tr>
<th><strong>The Client</strong></th>
<th><strong>Business Challenge</strong></th>
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<tbody>
<tr>
<td>• Well-financed public company with a differentiated preclinical cell-based platform capable of generating homogenous off-the-shelf engineered adoptive cell therapies (e.g. CART-, CAR-NK, etc.) that could be positioned across a range of cancer types and settings therein.</td>
<td>• Elucidate optimal positioning (targets, indications to be pursued) for an innovative but early-stage platform based on identification and consideration of key differentiating features of the platform within the context of extant unmet needs and the rapidly evolving competitive landscape.</td>
</tr>
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<table>
<thead>
<tr>
<th><strong>Our Approach</strong></th>
<th><strong>Valued Outcome</strong></th>
</tr>
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<tbody>
<tr>
<td>• Extensive analytics to identify a starting list of potential targets, along with scoring criteria, inputs, and supporting assumptions that reflect relevant scientific, clinical, and commercial considerations (including unmet need, market size of associated indications; user-friendly tool to generate rank-ordered lists of opportunities corresponding to differential weighting scenarios.</td>
<td>• Client provided with a well-supported tool to identify the most attractive targets and indications to be pursued with its ACT platform, including the ability to generate rank-ordered lists (and hence a diversified suite of candidates for consideration) associated with alternative corporate priorities such as speed to market, attractiveness to potential partners, or competitive gaps.</td>
</tr>
</tbody>
</table>
### Advanced Therapeutics

#### Recent Case Study: Strategic Development of Gene-Editing Platform Technology in Rare Disease Space

#### The Client
- US-based biotech with clinical stage best-in-class gene editing platform in development for various oncology settings
- looking to leverage the broad applicability of proprietary gene editing technologies to a broad range of human diseases beyond oncology

#### Business Challenge
- develop rational strategic plan for pursuing development of platform technology in areas outside of core oncology expertise
- prioritize therapeutic targets with genetic driver among the multitude of opportunities for gene editing within the rare disease space

#### Our Approach
- develop methodology for filtering rare genetic disease landscape based on selection criteria amenable to client platform technology
- map clinical stage gene therapy programs for genetic diseases with assessment of clinical value proposition

#### Valued Outcome
- pursuit of *ex vivo* cell-based development found to represent most attractive near-term opportunity in light of current regulatory and potential *in-vivo* delivery issues
- detailed profiles of 20 prioritized opportunities for client’s platform gene editing technologies within the rare disease space
## Advanced Therapeutics

### Recent Case Study: M&A guidance to support pipeline expansion

#### The Client
- clinical stage US biopharma with large market cap looking to implement portfolio expansion strategy
- client has single clinical stage asset & several discovery programs, aims to build pipeline that delivers new products to new rare diseases in rapid succession

#### Business Challenge
- identify M&A opportunities within rare disease space that align with client’s core capabilities, expertise and strategic focus
- filter list of selected opportunities that may be poised for acquisition – focus in ophthalmology disease

#### Our Approach
- profile leading and novel approaches for GT assets being developed for rare diseases with ophthalmologic phenotype
- solicit expert opinion on the potential of specific gene therapy technologies to address the unmet needs of patients with ophthalmologic disease

#### Valued Outcome
- Framework for vetting novel gene therapy opportunities within the rare sensory disorder space
- list of prioritized assets with recommended development plans including clinical endpoints and proposed strategic fit within client’s expanding portfolio
Rare Disease Consulting Team
Michael C. Rice, MS, MBA  
Principal  

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Mike heads Defined Health’s Advanced Therapies and Rare Diseases practices. He also co-heads the oncology practice focusing on hematologic malignancies and genetically defined cancers.

He has 20 years’ experience in biotech ventures defining strategic development and early commercial strategy for academic and biotech inventions pertaining to nucleic acids, gene therapy and cellular platforms applied across monogenetic diseases and oncology.

Mike studied molecular pharmacology, cancer genetics and the role of recombinational DNA repair enzymes such as RAD51 paralogs at Thomas Jefferson University’s Kimmel Cancer Institute. His thesis research led to pioneering gene editing technologies which served the basis of several gene therapy, diagnostics, and agribiotechnology firms. Mike holds an MBA, with a concentration in Biotechnology, from the Alfred Lerner School of Business and Economics, at the University of Delaware.

Mike is a member of the American Society of Gene and Cell Therapy (ASGCT), the Alliance for Regenerative Medicine (ARM), the Society for Immunotherapy of Cancer (SITC), the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), the Licensing Executives Society (LES), and the American Heart Association (AHA).
Joel S. Sandler, PhD
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As an Associate Principal and practice lead at Defined Health, Joel provides insight to various CNS and oncology therapeutics-focused clientele (biotechnology/pharmaceutical) on fundamental issues in drug development and partnering based on a comprehensive analysis of the key scientific, clinical, regulatory, and commercial questions relevant to the client’s particular situation.

In previous industry roles, Joel was instrumental in the scouting and evaluation of licensing and partnering opportunities for various oncology assets. Prior to his BD&L activities, Joel spent ten years focused on the discovery and characterization of bioactive compounds for cancer and infectious disease research at several leading academic institutions. His work has resulted in numerous grants, fellowships, patent filings, and peer-reviewed publications. He received his BA with honors from Cornell University, a PhD in Organic Chemistry from UCSD/Scripps, and was a NIH Postdoctoral Fellow at The Rockefeller University.

He is a member of numerous professional societies, including the American Academy of Neurology (AAN), American Neurological Association (ANA), the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the American Association for Cancer Research (AACR).
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As a Consultant with Defined Health, Brent participates in opportunity assessments, indication prioritization/sequencing, search, and strategy projects. Brent regularly contributes to projects in the cardiovascular, CNS, ophthalmology, dermatology, and AIID spaces.

Before joining Defined Health, Brent was a postdoctoral fellow in the Wu Center for Molecular Cardiology at Columbia University. As a postdoc at Columbia, Brent studied the molecular mechanisms of smooth muscle function, which led to the development of two novel mouse models of hypertension. In parallel to his time at Columbia, Brent worked as an analyst for The Solution Lab (TSL), a non-profit life sciences consulting firm in NYC. During his tenure with TSL, Brent advised clients in both pharma and biotech firms develop business strategies through competitive intelligence and quantitative analyses of niche markets.

Brent earned a PhD in Cell and Molecular Biology from the University of Vermont, in Burlington, VT, where his thesis focused on structure-function relationships of novel modulators of protein kinase activity. Brent also earned a BSc from UVM in Biological Sciences where he studied the mechanisms of microbial pathogenesis. Brent has published in peer-reviewed journals, presented his work at national and international scientific meetings and is co-inventor on a patent originating from his graduate studies.
Aruni S. Arachchige Don, PhD
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Aruni’s client work encompasses opportunity assessments, therapeutic area growth strategy and search projects, as well as the identification and evaluation of partnering opportunities. Since joining Defined Health in 2013, Aruni has contributed to projects that span the therapeutic landscape, with special emphasis on projects in respiratory diseases.

Prior to Defined Health, Aruni conducted translational research on targeting mTOR signaling for treatment of CNS injuries (e.g., traumatic brain and spinal cord injuries) and cancer. She is a published author of 7 peer-reviewed articles, including an expert review (in collaboration with Dr. Wise Young, the Founding Director of the W.M. Keck Center for Collaborative Neuroscience and a world renowned neuroscientist in the field of spinal cord injury at Rutgers University). Aruni completed a 3-year postdoctoral fellowship from the New Jersey Commission on Spinal Cord Research. During her postdoctoral tenure, Aruni also interned at the Office of Technology Transfer and Business Development, where she was involved in various aspects of business development and licensing and developed proficiency in evaluation and identification of novel technologies appropriate for commercialization. She is knowledgeable in the areas of intellectual property and technology transfer, the drug development process and related regulatory issues.

Aruni received a PhD in Pharmacology from the University of Iowa, Carver College of Medicine. She also earned Bachelor of Science degrees in both Biology and Microbiology from the University of Wisconsin, Madison and from the University of Minnesota, Twin Cities.
Akash Katakam
Senior Research Analyst

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Akash provides analytical support in opportunity assessments, indication prioritization, asset search and valuation, and corporate strategy projects. Akash works across several therapeutic areas at DH including oncology, advanced therapeutics (gene and cell therapies), respiratory, and CNS, among others. He co-authored Defined Health’s Cancer Progress 2017 Whitepaper, which addressed the emerging roles of immuno-oncology (IO) vs. non-IO therapies, collaboration vs. competition between oncology drug developers, and value vs. unmitigated pricing within the evolving oncology landscape. In addition, he focuses on expanding Defined Health’s market access, reimbursement, and pricing work and building DH’s presence in advanced therapeutics.

Prior to Defined Health, Akash worked in the biotech industry in a variety of roles. His experience includes working on the following teams: Life Sciences at the Technology Commercialization Office of the George Washington University (GWU), Global Healthcare Market Research at Penn Schoen Berland Associates, Biotechnology Investment Banking at Griffin Securities, where he assessed opportunities for a large biotech firm to partner with CAR-T companies and Waksman Institute of Microbiology at Rutgers University.

He holds three total publications to his name in the journal BMC Microbiology and at the National Center for Biotechnology Information (NCBI). He is also a co-founder of the GWU Biotechnology Club. Akash earned his Bachelor of Science in Biological Sciences and Economics degree with Honors from the George Washington University.
Since joining Defined Health in October 2017, Sonam has been exposed to both qualitative research and quantitative tasks across various therapeutic areas. The majority of her work has spanned the Gene Therapy, CNS and Oncology space.

Prior to Defined Health, Sonam worked with Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center where she gained extensive data analytical skills to facilitate healthcare organization and delivery.

Sonam received a B.A. in Biological Sciences from the University of Maryland and recently earned her M.S. in Health Informatics from Weill Cornell Medicine in New York. During her research thesis she explored drug-drug interaction alerts from a Clinical Decision Support perspective, analyzing ways to improve clinical workflow disruptions. Additional quantitative research projects included Natural Language Processing and Health Data Mining.
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