Reaching Forgotten Patients
Clinical Development & Commercial Perspectives

Eric Grinstead, Clementia
CBI PAP Meeting
Rare diseases are common and may result in significant morbidity

✦ 6 to 8 thousand distinct rare diseases*
✦ 80% of rare diseases are of genetic origin, and are often chronic and life-threatening*
✦ Estimated affected population
  – 25 million people in the US
  – 30 million plus in EU
✦ 340 drugs approved**

* [http://www.eurordis.org/about-rare-diseases](http://www.eurordis.org/about-rare-diseases)
** [http://www.ncats.nih.gov/about/faq/rare/rare-faq.html#What is a rare disease?](http://www.ncats.nih.gov/about/faq/rare/rare-faq.html#What is a rare disease?)
Outline

- The challenge of rare disease for patients and drug development
- Following the patient-centered healthcare sequence
- Integrating the clinical and commercial plans
- Summary
Small populations both face and create challenges

- Patient challenges
  - Low medical awareness
  - Missed diagnosis
  - Rarity of physicians
  - Lack of treatments

- Drug development challenges
  - Very few patients
  - Limited understanding of natural history
  - Uncertainty on disease activity markers and/or clinical trial endpoints
  - Compression of development timelines
Rare diseases are not always obvious

Leonardo da Vinci, 1503-1506

Priceless

Mark Rothko, 1950

$74.9 million, 2006

Jackson Pollack, 1948

$148.1 million, 2007

Jasper Johns, 1959

$80 million, 2006

Leonardo da Vinci, 1503-1506
It takes evidence to change management of a rare disease, but...

- Clinical experience is in short supply
  - Scientific rationale or abstract conceptualizing are not as credible as clinical evidence
  - N = 1 does not enable experiential learning
- Clinical trials are complicated
  - Bringing the patient to the trial or the trial to the patient
    - Sparse sites, all comers, family relocations
    - Extension sites
  - Limited existing information
    - Phenotypic heterogeneity
    - Disease progression
    - Relevant endpoints, biomarkers
Development timelines for rare disease may get compressed

**Common**

Duration clinical studies 5-10 years

Exploratory clinical development plan

Clinical development and commercial plan

**Rare**

Duration clinical studies < 5 years

Small patient numbers and compression of timelines requires thoughtful integration of clinical development and commercial plans
Outline

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- Summary
A patient-centric development plan begins with careful examination of the healthcare transaction.

**PREVALENCE**
- Individual is born with mutation, acquires mutation, suffers injury or develops disease

**1. DIAGNOSIS**
- Patient ...
  - Experiences signs/symptoms
  - Seeks medical help
  - Is referred to physician who is capable of diagnosis
  - Is confirmed with diagnosis

**2. TREATMENT**
- Patient-Physician ...
  - Agree on the serious nature of the disease
  - Review treatment options and prognosis
  - Agree to treat

**3. COVERAGE**
- Payor...
  - Reviews request
  - Approves, denies or request more info
  - Physician/patient provide more info
  - Payor approves/denies
  - Patient/physician appeal, up to 5 cycles of appeals

**4. ADHERENCE**
- Patient-physician-treatment site
  - Schedules set/maintained for patient treatment
  - Patient attends treatment session and is treated
  - F/U begins to perpetuate the cycle
Identifying patients and supporting accurate diagnosis is a commercial imperative that begins in the clinical stage.

**Commercial capability:** raise awareness & educate

1. **DIAGNOSIS**
   - **Patient ...**
     - Experiences signs/symptoms
     - Seeks medical help
     - Is referred to physician who is capable of diagnosis
     - Is confirmed with diagnosis

2. **TREATMENT**
   - **Patient-Physician ...**
     - Agree on the serious nature of the disease
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- Path to diagnosis
  - Physician specialty
- Differential
  - Index of suspicion
- Confirmatory lab tests
  - What is the technology
  - Who can do it
  - How do they connect to the clinic
Initial work-up directs the patient journey and informs both clinical & commercial plans...

Physician Exam:
1. Interview
   • History
   • Signs/symptoms
2. Physical Exam
3. Lab tests
4. Diagnosis
5. Treatment
6. Referral

Lab Tests:
1. ?
2. ?

Treatment:
1. Prescription
2. Diet
3. Other palliative measures

Referral:
1. To Who
2. With what information
Low awareness risks wrong referral and delay of diagnosis
Raising physician awareness is a commercial imperative that begins in the clinical stage

Commercial capability: raise awareness & educate

1. DIAGNOSIS
   Patient ...
   ✦ Experiences signs/symptoms
   ✦ Seeks medical help
   ✦ Is referred to physician who is capable of diagnosis
   ✦ Is confirmed with diagnosis

2. TREATMENT
   Patient-Physician ...
   ✦ Agree on the serious nature of the disease
   ✦ Review treatment options and prognosis
   ✦ Agree to treat

✦ Serious disease
  – Natural history
    ✦ Risk of not treating
  – Irreversible damage
  – Risk profile by phenotype
    ✦ Profile of patients most likely to benefit

✦ Effective treatment
  – Natural history
    ✦ Inadequacy of current treatments
  – Need for early and ongoing interventions
  – Effectiveness of new treatment
    ✦ Benefit profile by phenotype
Securing access is a commercial imperative that begins in the clinical stage

**Commercial capability:** connect & serve

- **Physicians & Patients**
  - Evidence for medical necessity
  - Local, regional and national physician and patient advocates
  - Clarity on the rules for insurance, coverage and reimbursement
  - Assistance and reimbursement support programs

- **Payors**
  - Evidence for medical necessity
  - Dossier
    - Burden of illness, modeling
  - Code loading and automated systems updates
  - Patient insurance benefits
  - Denial-appeals escalation path
    - 3rd party adjudication board

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### 3. COVERAGE

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### 4. ADHERENCE

**Patient-physician-treatment site**
- Schedules set/maintained for patient treatment
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- F/U begins to perpetuate the cycle
Appropriate utilization is a commercial imperative that begins in the clinical stage

Commercial capability: connect & serve

- Education
  - Registry data, disease severity indices, biomarker programs

- Treatment support programs
  - Clarity on the rules for insurance, coverage and reimbursement
  - Assistance and reimbursement support programs

- Pharmacovigilance & REMs programs
  - Collecting data

4. ADHERENCE

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An integrated clinical/commercial plan facilitates development of a therapeutic community

- The clinical plan documents the benefits of a medical transaction in a controlled environment
  - Generates data
  - Identifies physicians and medical community
  - Affirms diagnostic process
  - Documents treatment benefit and organizes evidence

- The commercial plan enables the reproduction of the medical transaction in an uncontrolled market environment
  - Communicates data
  - Identifies patients and disseminates diagnostic policy
  - Educates and inspires physicians
  - Secures reimbursement
  - Manages logistics, supply, support and adherence

...ensuring right patient is treated with right dose at right interval
The clinical plan functions as a an instruction manual for the market

- **Natural history**: Documents need by qualifying and quantifying morbidity/mortality of untreated disease
- **Diagnostic criteria**: Sets baseline for developing and disseminating diagnostic policy and tools
- **Physician identification**: Initiates awareness, recognizes KOLs, establishes medical community, builds champions
- **Patient identification**: Enables community by connecting patients to providers and building up patient groups
- **Protocols**: Anticipates effect becoming the antecedent to market-based treatment policy and plans
- **Reports**: Communicates benefit and supports label/evidence including diagnostic and treatment publications, practices and protocols
Label and indication ARE paramount

- TPP description of indication statement
  - Indicated in/for the treatment or prevention of a recognized disease or condition
  - Indicated for the relief of symptoms associated with a disease or syndrome
  - Indicated for a particular indication only in conjunction with a primary mode of therapy

1. Sets parameters for disease communication
   - Influences ability to drive

2. Sets parameters for coverage
   - Influences ability to pull-thru

3. Sets focus and directionality for development
   - Improves efficiency of resource utilization
The Blue’s technology evaluation center criteria provides guidance for evidence development

- The therapy must have final approval from the appropriate governmental regulatory bodies
- The scientific evidence must permit conclusions concerning the effect of the therapy on health outcomes
- The therapy must improve the net health outcome
- The therapy must be as beneficial as any established alternatives
- The improvement must be attainable outside the investigational settings

http://www.bcbs.com/blueresources/tec/tec-criteria.html
Anticipating coverage resources for under and uninsured patients post approval

<table>
<thead>
<tr>
<th>Problem</th>
<th>Lack coverage</th>
<th>Problems with coverage</th>
<th>Access to coverage</th>
<th>Under-insured</th>
<th>Strapped</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LTM, Annual Max</td>
<td>Short term duress</td>
<td>Cannot afford premium</td>
<td>Cannot afford out-of-pocket costs</td>
<td>Cannot cover the associated costs of treatment</td>
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<tr>
<td></td>
<td>Transitions</td>
<td>Study transitions</td>
<td></td>
<td>Cannot leverage coverage</td>
<td>Travel, infusion charges, etc.</td>
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<tr>
<td></td>
<td>Chronically uninsured</td>
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<thead>
<tr>
<th>Resources</th>
<th>Charitable Assistance</th>
<th>Interim Assistance</th>
<th>Premium Assistance</th>
<th>Out-of-Pocket Assistance</th>
<th>Ancillary Assistance</th>
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<thead>
<tr>
<th>Decisions</th>
<th>Eligibility criteria</th>
<th>Award</th>
<th>Accounting treatment</th>
<th>Who</th>
<th>Funding agreement for grant</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No insurance</td>
<td>Incorporation</td>
<td>Incorporation</td>
<td>HealthWell</td>
<td>3rd Party Foundations</td>
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<tr>
<td></td>
<td>No access to insurance</td>
<td>501(c)3 (tax filings)</td>
<td>501(c)3 (tax filings)</td>
<td>PANF</td>
<td>Financial eligibility</td>
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<tr>
<td></td>
<td>Income</td>
<td>Board appointees</td>
<td>Board appointees</td>
<td>PSI</td>
<td>Other eligibility requirements</td>
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<tr>
<td></td>
<td>Assets</td>
<td></td>
<td></td>
<td>NORD</td>
<td>Award levels</td>
</tr>
<tr>
<td></td>
<td>Spend down</td>
<td></td>
<td></td>
<td>PAF</td>
<td>Staff and other resources</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>CDF</td>
<td>Application and other forms</td>
</tr>
</tbody>
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|                   | Spillover                      | Management                  |                           |                               |                                   |
|                   | Interim program                | US Access Services & CMP    |                           |                               |                                   |
|                   | No interim program             |                              |                           |                               |                                   |

- **LTM**: Long Term Maintenance
- **Max**: Maximum
- **LTC**: Long Term Care
- **TS**: Transitions
- **PANF**: Pancreatic Cancer Action Network Foundation
- **NORD**: National Organization for Rare Disorders
- **PAF**: Patient Advocate Foundation
- **CDF**: Children’s Defense Fund
Where there’s a will there’s a way to connect patients to treatment

<table>
<thead>
<tr>
<th>Pre-Approval</th>
<th>Post-Approval</th>
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<tbody>
<tr>
<td>✦ Funding</td>
<td>✦ Funding</td>
</tr>
<tr>
<td>– Clinical trial distribution</td>
<td>– Govt: agency/contractor</td>
</tr>
<tr>
<td>– Named patient sales</td>
<td>– Private: insurance carrier</td>
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<tr>
<td>– Compassionate use</td>
<td>– Charity:</td>
</tr>
<tr>
<td>– Others...</td>
<td>☰ Company sponsored patient assistance program</td>
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<tr>
<td></td>
<td>☰ 3rd party foundation</td>
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<thead>
<tr>
<th>Regulation</th>
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<tbody>
<tr>
<td>☐ Import/export requirements &amp; logistics</td>
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<tr>
<td>☐ Release requirements (quality assurance)</td>
</tr>
<tr>
<td>☐ Licensure reciprocity, etc.</td>
</tr>
<tr>
<td><strong>Dynamics vary by country/region</strong></td>
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Challenges to a chronic, life-long treatment plan require solutions

- Likelihood of response
  - Impact on survival
  - Impact on overall well-being
- Medical events
  - Non-response
  - Hospitalizations or other medical interruptions
- Treatment site venue change
  - Vacation, job travel
- Site logistics
  - Spoiled product
  - Weather
  - Unscheduled interruption to hours
- Life changes
  - Marriage, divorce, job change, relocation, pregnancy, retirement, death
  - Moving out of country or State
Multiple approaches to launching in rare disease indication

- Partnerships with companies who have commercial infrastructure
- Outsourced reimbursement and distribution capabilities
- Build in-house commercialization capabilities
Outline

- The challenge of rare disease for patients and drug development
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Summary
Development Of Therapeutic Structure

Drug-centric development model tends to be linear...

Lab
Identifies Drug Candidate

Clinic
Develop Evidence To Differentiate The Candidate

Market
Integrate Candidate Into Existing Therapeutic Structures

Patient-centric development model is quite dynamic...

Lab
• Evaluates Unmet Need
• Identifies Drug Candidate

Clinic
• Natural History
• Diagnostic Tools
• Medical Evidence
• Physician/patient communities

Market
Launch A New Therapeutic Area
Thank you. I would now like to return the program to Art...