The FDA and Unmet Needs:

The Path to New Therapy for Transplant Recipients

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Disclosures

- Ad Board—Novartis, Roche, Astellas
- Mayo Contract—Transplant Genomics, Inc.

Unmet Needs

Transplantation is not perfect

- Long-term outcomes of all organs, but especially kidney, pancreas, heart and lung
- Toxicities of immunosuppression—nephrotoxicity, diabetes, cancer, infection
- Antibody barriers to transplantation

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Personal Viewpoint

Developing New Immunosuppression for the Next Generation of Transplant Recipients: The Path Forward

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AJT 2016; 16:1094-1101

Barriers to new therapy

- FDA – 1 year graft and patient survival as an endpoint
- Industry – Views transplantation as a small field, too many reportable complications may tarnish the reputation of a drug used in autoimmunity or other fields
- Transplant Community – fragmented, unable to speak with one voice
- All – belief that current outcomes are great

Transplant is a small field (and not “special”)

- 23,000 clinical trials ongoing today
- 17,000 are in cancer
- ?20-30 in transplant

The Food and Drug Administration

- Approves all new drugs in the US

Evidence-based criteria

- Safety
- Efficacy

The FDA approves new drugs

- For a specific indication
- Prospective, randomized trials (prefers 2)
- Clear inclusion criteria
- Clear endpoints
- A problem in fields with few patients

How many drugs are FDA approved?

Year	Approvals	Total
1938-2014		1453
2014	41	1494
2015	45	1539
2016	22	1561
2017	5	1566

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm

http://www.raps.org/Regulatory-Focus/News/2014/10/03/20488/How-Many-Drugs-has-FDA-Approved-in-its-Entire-History-New-Paper-Explains/

How many drugs are FDA approved?

No.	Drug Name	Active Ingredient	Approval Date	FDA-approved use on approval date
5	Xermelo	telotristat ethyl	2/28/2017	To treat carcinoid syndrome diarrhea
4.	Siliq	brodalumab	2/15/2017	To treat adults with moderate-to-severe plaque psoriasis
3.	Emflaza	deflazacort	2/9/2017	To treat patients age 5 years and older with Duchenne muscular dystrophy (DMD)
2.	Parsabiv	etelcalcetide	2/8/2017	To treat secondary hyperparathyroidism in adult patients with chronic kidney disease undergoing dialysis
1.	Trulance	plecanatide	1/19/2017	To treat Chronic Idiopathic Constipation (CIC) in adult patients.

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm

Clinical Endpoints: Definition

- How a patient feels, functions or survives
- In transplant: 1 year patient and graft survival and biopsy proven acute rejection.
- In the end, most new drugs will be approved only if they increase graft survival.

Improving Graft Survival

- Difficult to improve 1 year graft survival
- Long-term studies are difficult and expensive
- Common problem in almost all fields of medicine
- Surrogate endpoints/predictive biomarkers

Subpart H: Interim Approval

- Shortens time to approval
- Encourages companies to study long-term outcomes
- Drug gets FDA interim approval because it improves a predictive biomarker
- Drug can then be marked and sold
- Follow-up studies needed to show that it actually improves the clinical endpoint (ex. graft survival)
- May be “pulled” if it does not meet the clinical endpoint

Accepted predictive biomarkers/surrogate endpoints for drug-approval trials

- HbA1c
- Reduction in tumor volume
- Reduction in HIV viral load.
- No predictive biomarker is approved as a surrogate endpoint for graft loss in transplantation

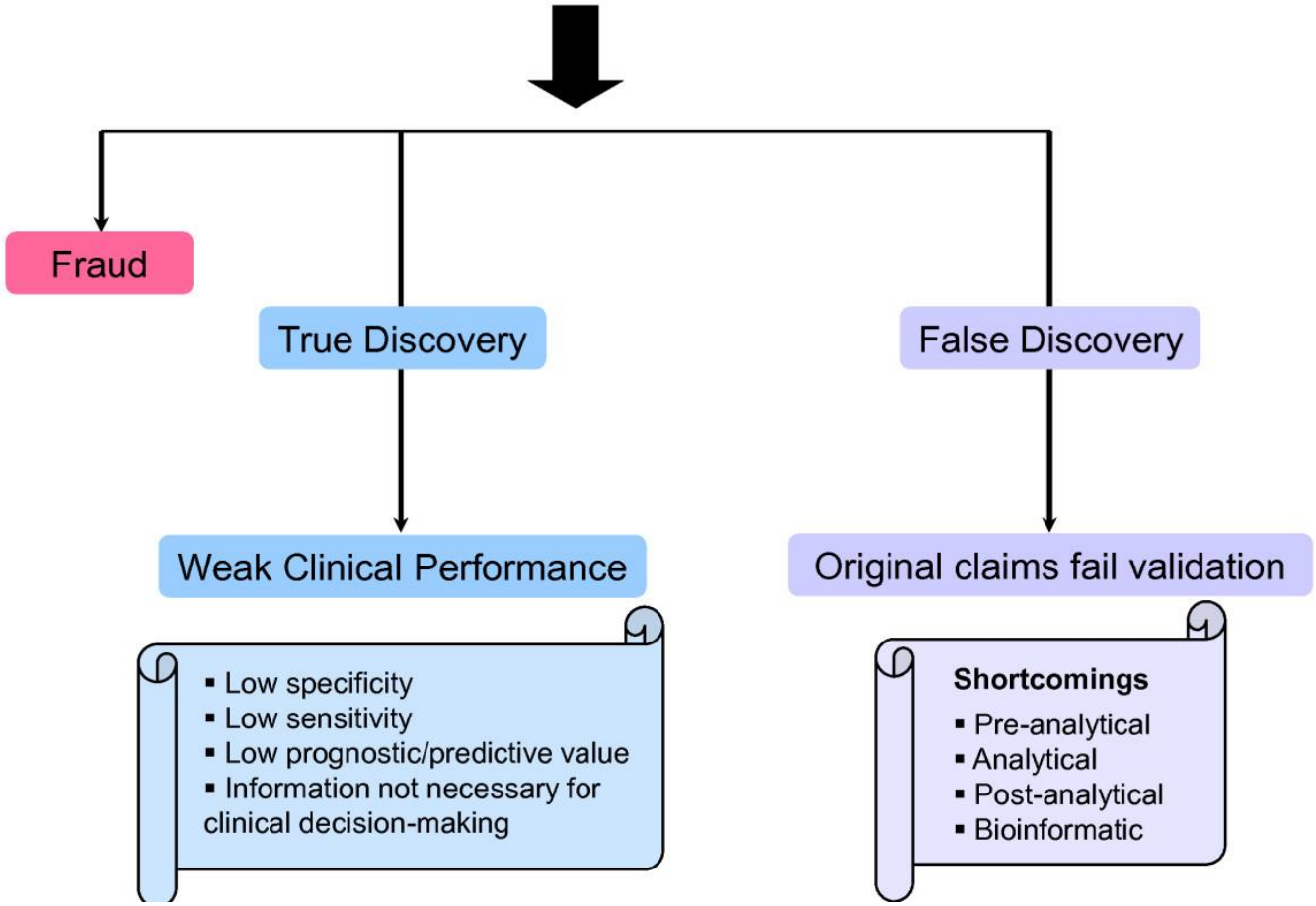
The FDA has a long history with poor-performing biomarkers

- Cholesterol—poor correlation with heart attacks, stroke and death
- PSA--?too many false positive results

The FDA has a long history with poor-performing biomarkers

- Thus, they will want strong data showing:
- There is a high correlation between the biomarker (ex. acute active antibody mediated rejection per Banff 2013) and subsequent graft loss
- Biomarker should be “in the pathway of the disease”
- Thus, they are wary of eGFR as a predictive biomarker
- Too many factors affect eGFR and the correlation between eGFR and graft loss is low

Why Biomarkers Fail to Reach the Clinic



*EP Diamanidis BMC Medicine*2012**10**:87

Clinical Chemistry 59:1
202–204 (2013)

Opinions

Biomarker Failures

John P.A. Ioannidis[1,2,3*]

The quest for biomarkers has been a highly prolific, exciting field of research. Despite major promises, however, that biomarkers can improve diagnosis, prognosis, prediction, overall management, and eventually the health outcomes of single people and many

able reclassification into risk categories in which the optimal managements would be different. Overdiagnosis rates were as high as 17%–50%, and treatment could produce serious harms. Extensive research was eventually performed, often from teams that explicitly

Remember:

These are mostly cancer/cardiovascular biomarkers with thousands of patients to study validation

Most biomarkers are not validated and are therefore worthless

- 21st Century Cures Act
- Push for the FDA to accept more biomarkers

The Goal

To identify a predictive biomarker that

- Has a very high correlation with graft loss in the subsequent 1-3 years (ex. >35% fail)
- Represents a process that can either be stabilized or reversed
- Is common enough that a clinical trial can be performed with enrollment in 2 years.

Transplant Therapeutics Consortium, Coordinating Committee Meeting

AST AMERICAN SOCIETY OF TRANSPLANTATION

ASTS American Society of Transplant Surgeons

TTC TRANSPLANT THERAPEUTICS CONSORTIUM

CRITICAL PATH INSTITUTE

Transplant Therapeutics Consortium

- Joint venture between ASTS, AST, Industry and the FDA
- Address the barriers to developing new therapy for transplant recipients
- Managed by the Critical Path Institute

Membership

- Money needed for management and studies
- $55 K for Industry market cap >$1 billion
- $25 K for Industry <$1 billion, Societies, non-profits
- Each member gets one vote on the Coordinating Committee
- Currently approximately 8 members

Setting Attainable Goals

1) Four Preliminary themes

- Regulatory & Trial Design
- Adverse Event Reporting
- Patient-Reported Outcomes
- Institutional Concerns

2) Further Stratification

- Breaking these into short and long-term deliverables based on
  - Regulatory agency appetite
  - Timeline for completion
  - Availability of suitable supporting historical data
  - Workgroups

– Wide participation from all in transplant community

TTC

- Biomarker Work Group: To consider any biomarker for any outcome
- “Molecular microscope”
- Peripheral blood assays (TruGraf, etc)
- C1q, MFI quantification
- A forum for evaluating current data and building consensus regarding biomarkers and endpoints

Challenge for Banff 2017 Meeting

- Histology is the cornerstone of diagnosis (and prognosis) in nephrology and kidney transplantation

Assumptions: Histology as a Biomarker

- Already used by the FDA (precedent)—ex. BPAR in 1st year
- Does not require approval of a new assay (involving other parts of the FDA)
- Will require studies that validate histology as a biomarker and a consensus among experts
- Might be the pathway to validating other biomarkers (genomics, proteomics, etc).

Goal

- Go to the FDA with data and a consensus regarding specific, reversible histologic lesions
- Active ABMR, cABMR
- Borderline, subclinical rejection

Is there interest in working on this?

Thank you!