Immunoassays in Multiplex for Personalized Medicine

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Drug Safety

(Critical Path Initiative)

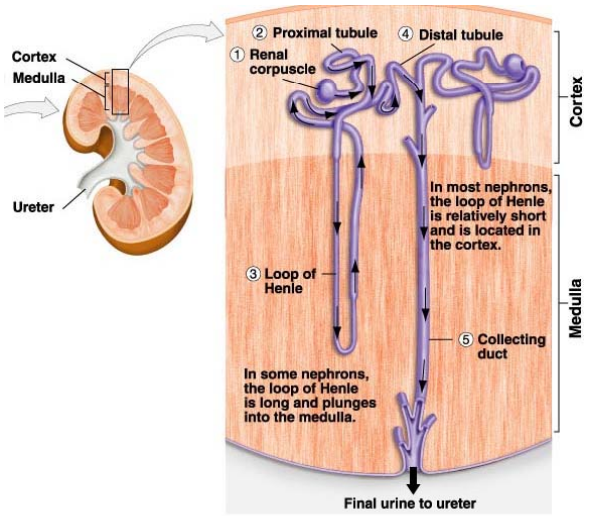
Predictive Safety Testing Consortium

RBM
RULES • BASED MEDICINE

Antibody based Biomarker assays

- FDA Critical Path Initiative
- Predictive Safety Testing Consortium (PSTC)
- 7 urinary biomarkers for drug induced kidney injury submitted for FDA approval

Nature Biotechnology ***28, May 2010***



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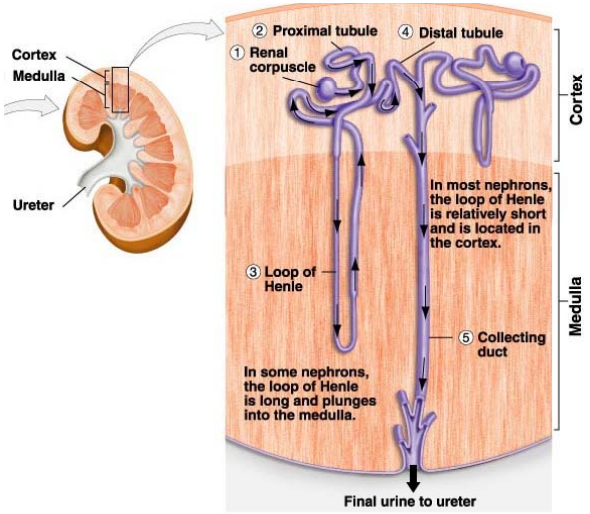
Antibody based Biomarker assays

- Rat Nephrotoxicity Panel
- Rules Base Medicine / Luminex Array

1. **β-2 Microglobulin**
2. Calbindin
3. **Clusterin**
4. **Cystatin-C**
5. Epidermal Growth Factor (EGF)
6. Glutathione S-Transferase-alpha (GST-α)
7. Glutathione S-Transferase-pi (GST-Π)
8. **Kidney injury molecule 1(KIM1)**
9. Neutrophil Gelatinase Associated Lipocalin (NGAL)
10. Osteopontin
11. Tissue Inhibitor of Metalloproteinase-1 (TIMP-1)
12. Vascular Endothelial Growth Factor (VEGF)



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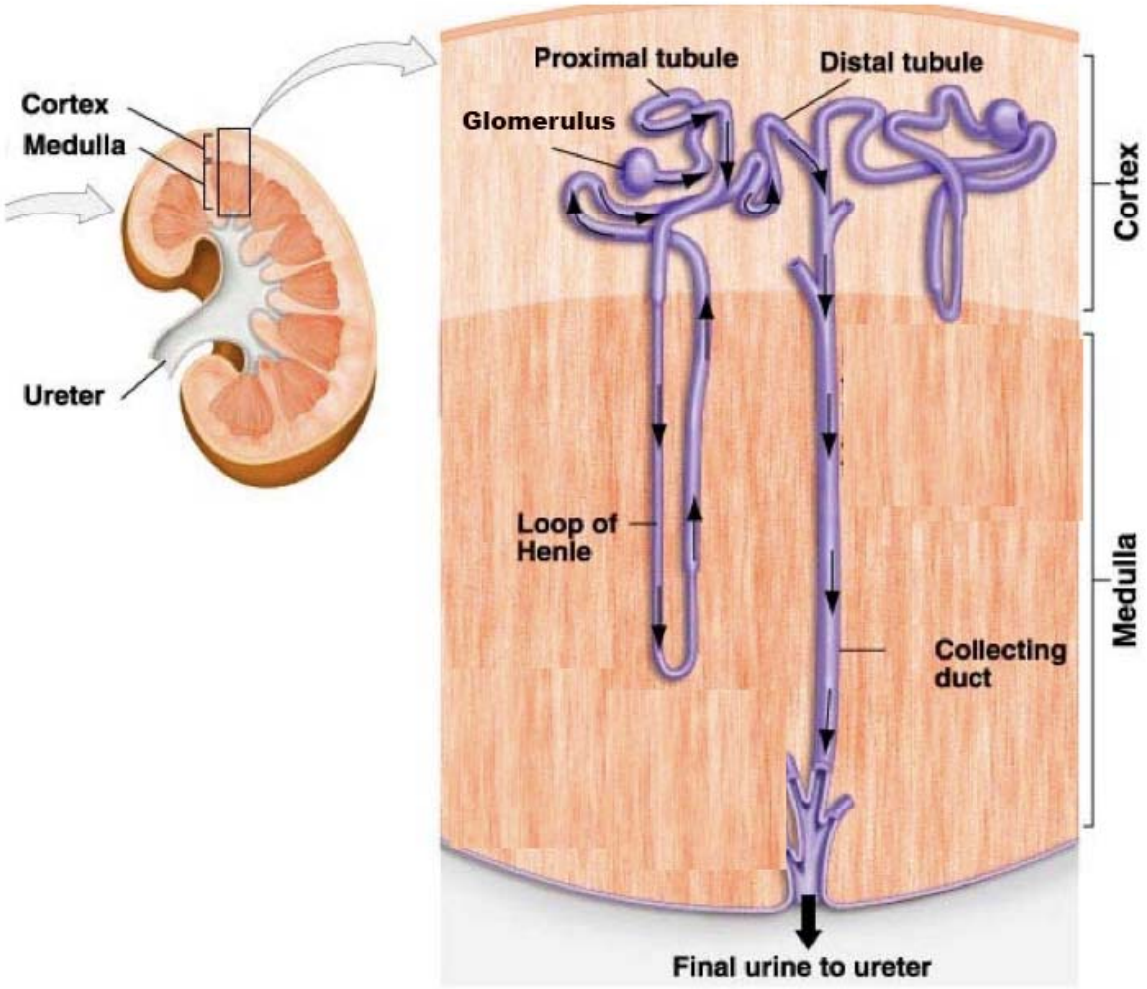
Kidney Toxicity Standard



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Proximal Tubules

- Alpha –GST
- KIM-1
- Clusterin
- Osteopontin
- ß-2-microglobulin
- Calbindin d28
- NAG
- TIMP-1

Distal Tubules

- mu GST
- KIM-1
- Clusterin
- Osteopontin
- TIMP-1

Glomeruli

- ß-2-microglobulin
- Podocin

The Innovative Medicine Initiative
Safer & Faster Evidence Based Translation project

Qualification of new specific and sensitive safety biomarkers for drug-induced

Kidney 

Liver 

Vascular 

injury to improve safety of drug development

SAFE-T

imi

Academia

NMI achieving results

Assistance Publique Hôpitaux de Paris

Charité

Icccc Institut Català de Ciències Cardiovasculars

CSIC

The Tel Aviv Sourasky Medical Center

EFPIA

AstraZeneca

Novartis

Pfizer

Roche

Bayer HealthCare Bayer Schering Pharma

sanofi aventis

gsk GlaxoSmithKline

Almirall

Amgen

Lilly

Advisors

European Medicines Agency Science Medicines Health

FDA

SMEs

Firalis

Interface Europe

Argutus Medical Making a Mark in Medicine

EDI Experimentelle & Diagnostische Immunologie GmbH

Collaborators

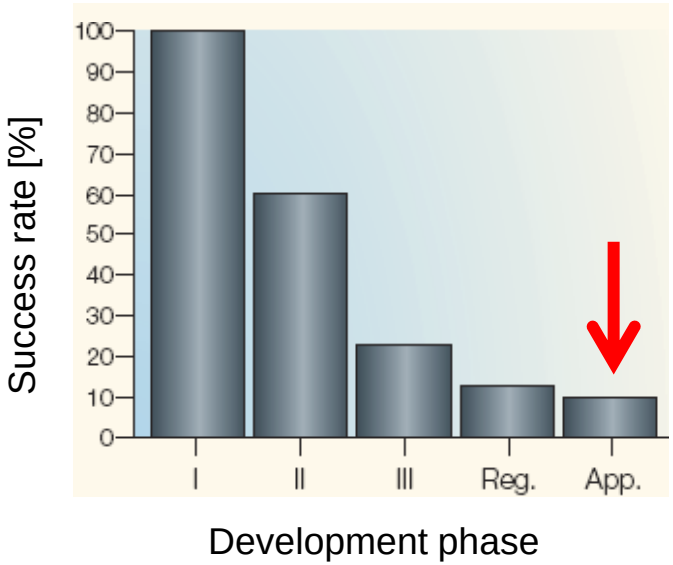
Uma Universidad de Málaga

University of Liverpool

PSTC Critical Path Institute

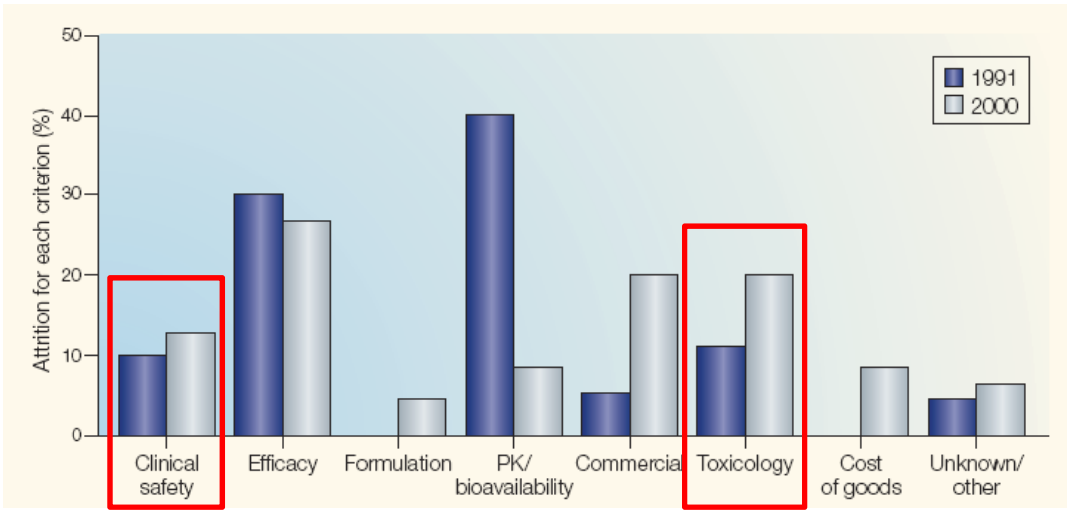
Drug safety: room for improvement

The economic perspective



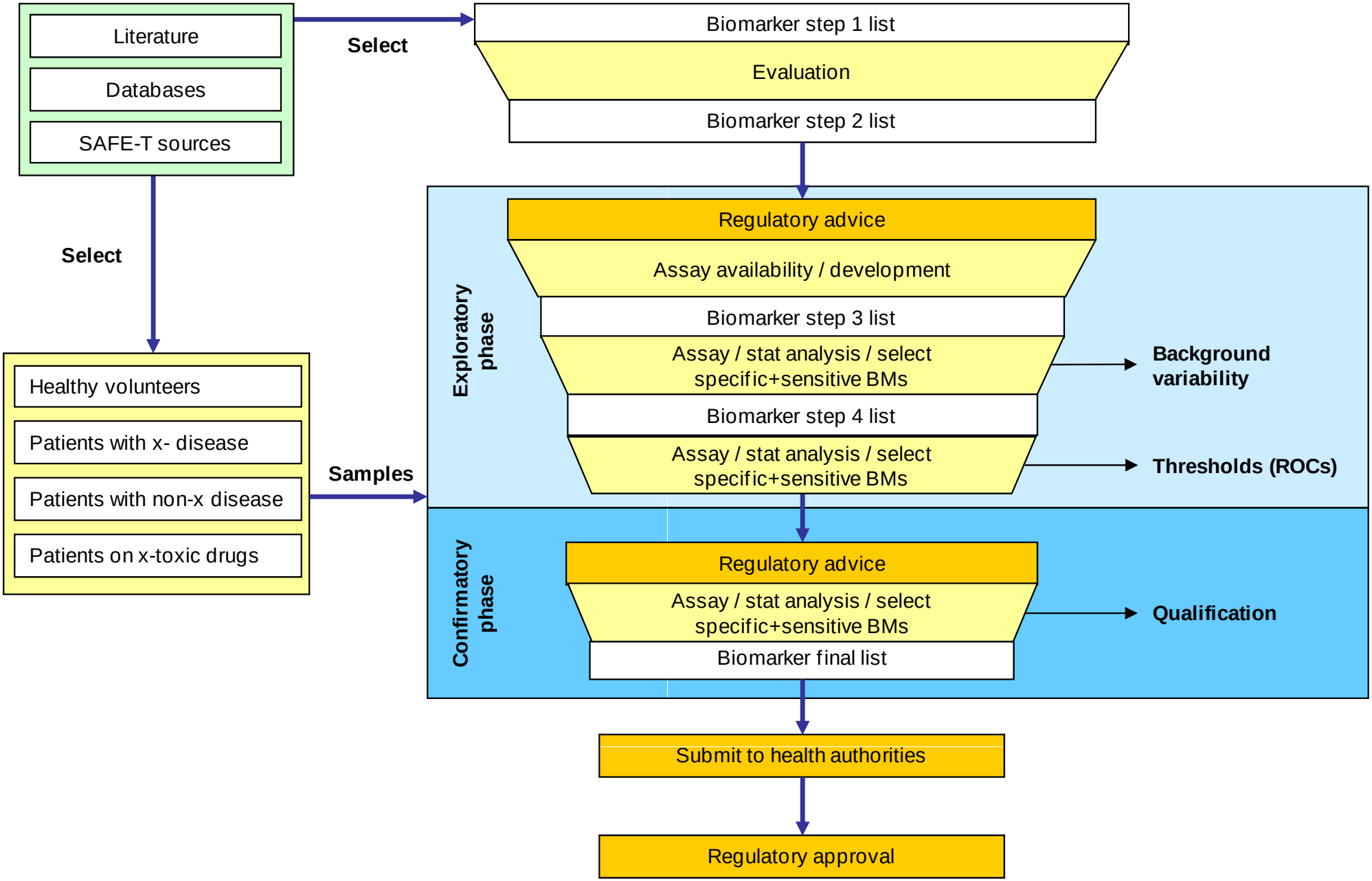
- Around 90% of compounds entering clinical development fail

- 30% of these failures are due to clinical safety and toxicology

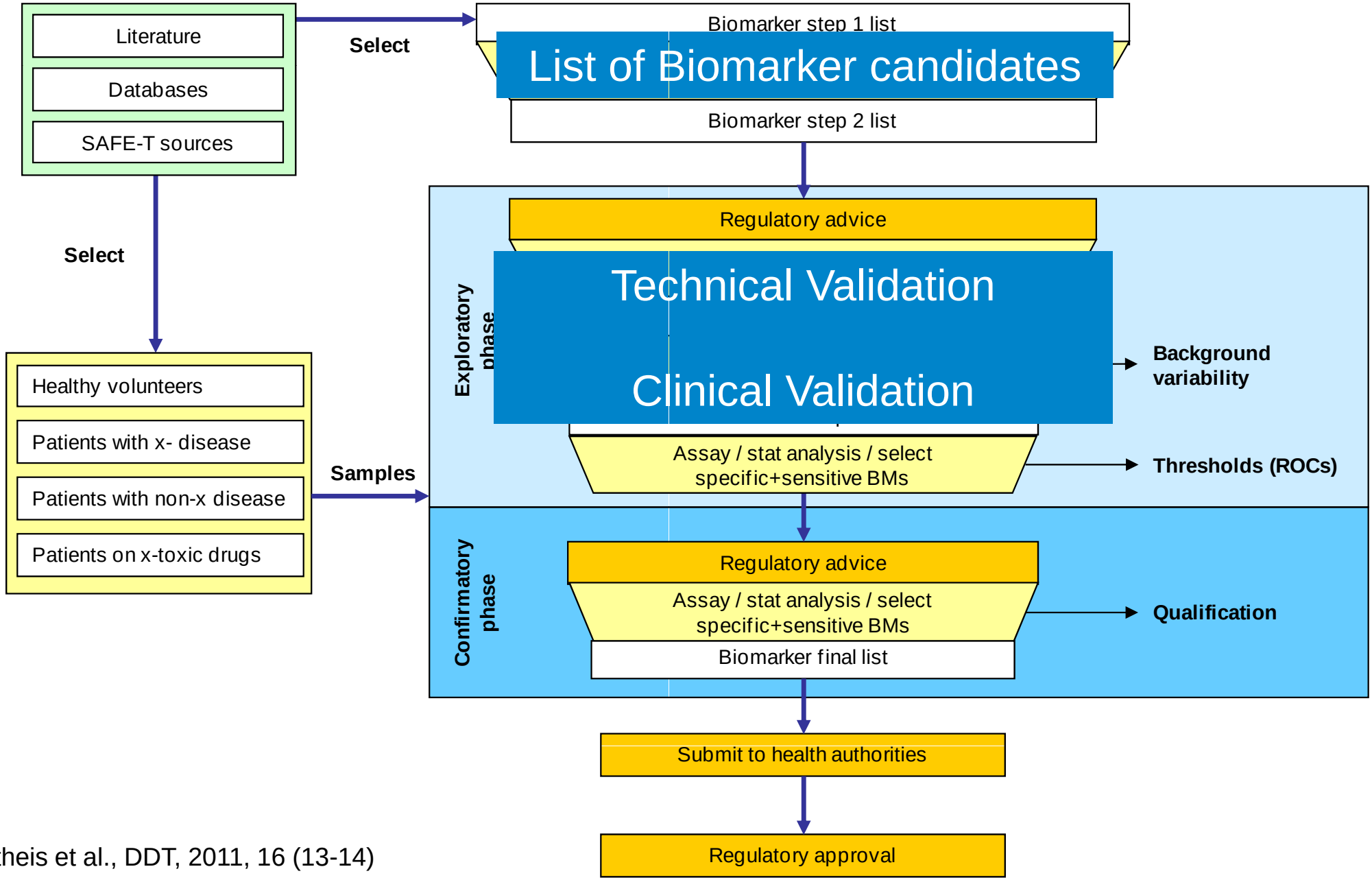


Kola et al. (2004), Nat Rev Drug Discovery ; 3: 711-15

The Innovative Medicine Initiative
The SAFE-T project:



The Innovative Medicine Initiative
The SAFE-T project:



Matheis et al., DDT, 2011, 16 (13-14)

DILI biomarker candidates selected for qualification

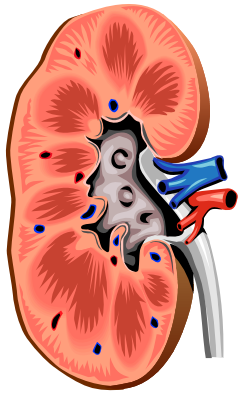
- *Drug Induced Liver Injury* is a rare event, sample availability is limited

Serum or Plasma Marker	Assays	Liver specificity	Human data	Pathology
miRNA 122	RNA / QPCR	highly specific	yes	heptocellular damage
albumin mRNA	RNA / QPCR	highly specific	yes	heptocellular damage
Microglobulin precursor (Ambp) mRNA	RNA / QPCR	highly specific	yes	heptocellular damage
High mobility group box 1 (acetylated vs. non-acetylated)	LC-MS	not specific	yes	cholestasis
Conjugated/unconjugated bile acids	LC-MS	highly specific	only in tissue	heptocellular damage
F-protein (HPPD)	Immunoassay	highly specific	yes	heptocellular damage
Arginase 1	Immunoassay	highly specific	yes	heptocellular damage
Keratin 18 (caspase cleaved & intact)	Immunoassay	not specific	yes	heptocellular damage
Alpha fetoprotein (AFP)	Immunoassay	specific	yes	heptocellular damage
Regucalcin (RGN)	Immunoassay	specific	only in tissue	heptocellular damage
Glutathione S-Transferase (GST-alpha)	Immunoassay	specific	yes	heptocellular damage
ST6gal I	Immunoassay	specific	yes	inflammation
Osteopontin	Immunoassay	not specific	yes	inflammation
Colony stimulating factor receptor (CSF1R)	Immunoassay	not specific	yes	inflammation
LECT2	Immunoassay	not specific	yes	inflammation
Paraoxonase 1 (PON1)	Immunoassay	not specific	yes	steatosis
Prothrombin	Immunoassay	not specific	yes	steatosis
Glutamate dehydrogenase (GLUD, GLDH)	Enzyme activity	specific	yes	heptocellular damage
Sorbitol dehydrogenase (SDH)	Enzyme activity	specific	yes	heptocellular damage

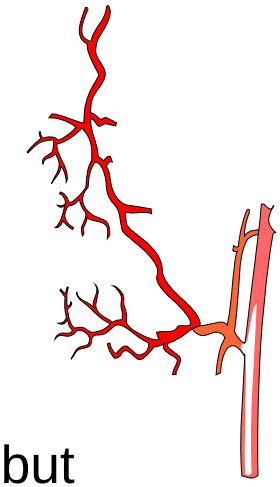
Composite disease markers to be assessed in addition: ActiTest™, Fibrotest™, SteatoTest™

SAFE-T

- **DIKI**
  - 21 biomarkers listed for evaluation in SAFE-T
  - For some markers results available from preclinical experiments (PSTC)
  - All biomarkers are now tested with samples from clinical studies



- **DIVI**
  - Not much known about potential biomarkers
  - 35 potential biomarkers were chosen for evaluation



→ Identified biomarkers will not only be applied in drug development, but might also be used for personalized medicine.