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# Drug Safety



## (Critical Path Initiative)

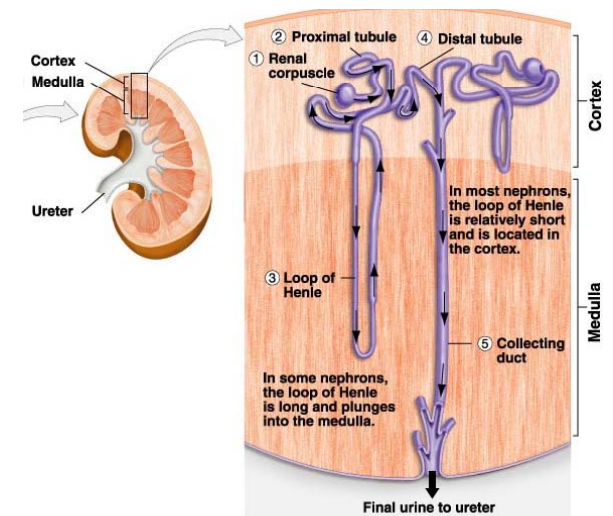
### Predictive Safety Testing Consortium



# 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

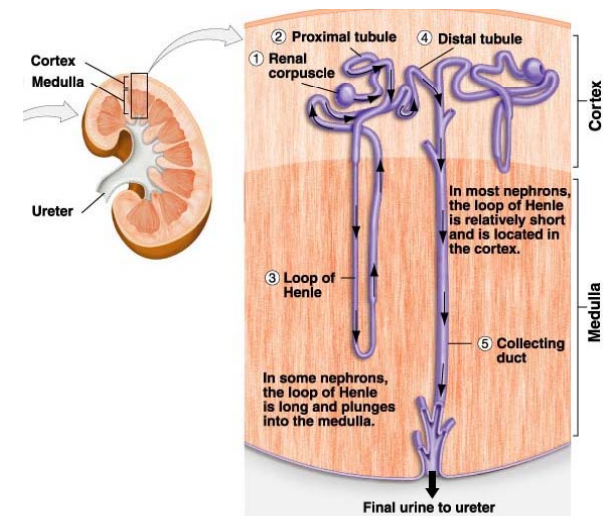


<http://www.uic.edu/classes/bios/bios100/lecturesf04am/kidney01a.jpg>

# Antibody based Biomarker assays

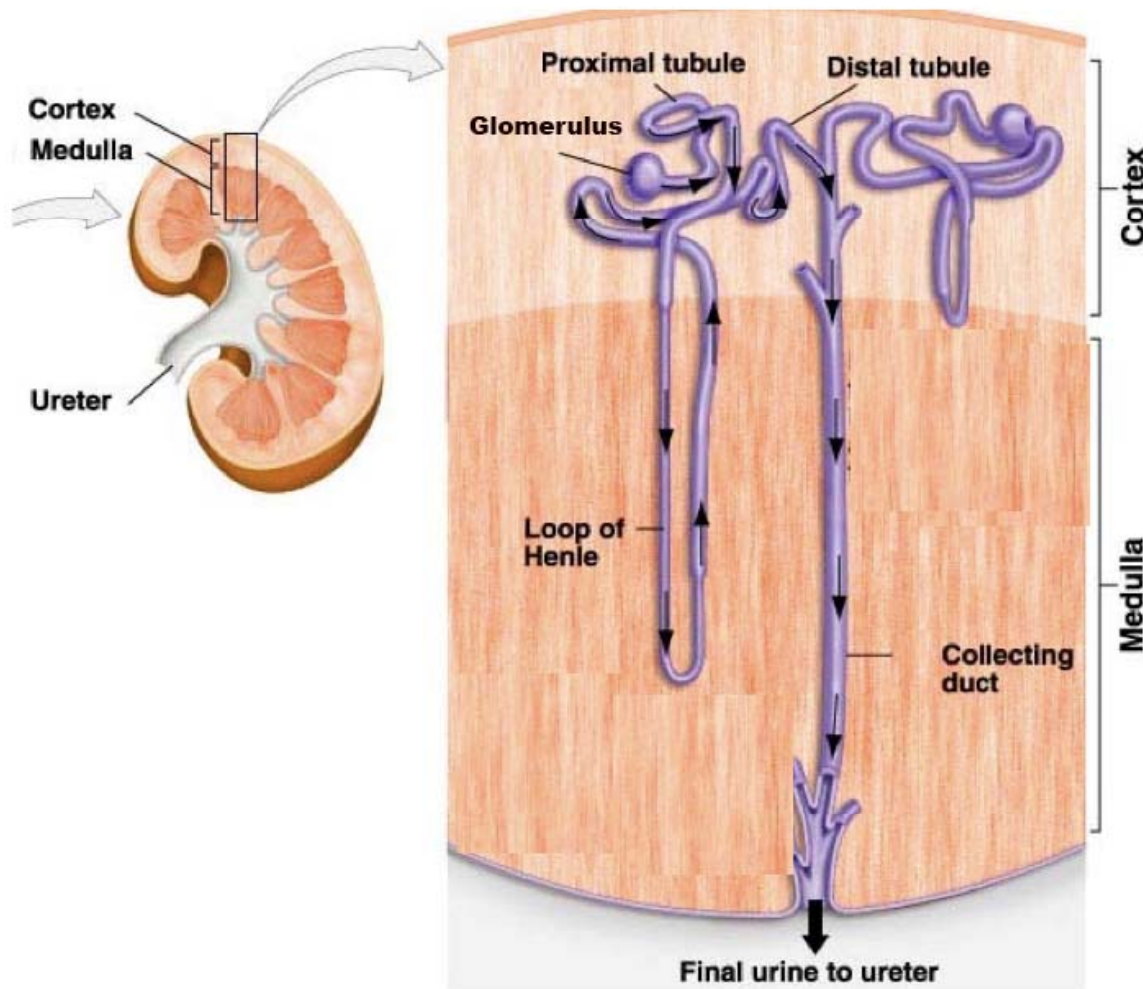
- Rat Nephrotoxicity Panel
- Rules Base Medicine / Luminex Array

1.  $\beta$ -2 Microglobulin
2. Calbindin
3. Clusterin
4. Cystatin-C
5. Epidermal Growth Factor (EGF)
6. Glutathione S-Transferase-alpha (GST- $\alpha$ )
7. Glutathione S-Transferase-pi (GST- $\Pi$ )
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)



<http://www.uic.edu/classes/bios/bios100/lecturesf04am/kidney01a.jpg>

# Kidney Toxicity Standard



## Proximal Tubules

- Alpha -GST
- KIM-1
- Clusterin
- Osteopontin
- $\beta$ -2-microglobulin
- Calbindin d28
- NAG
- TIMP-1

## Distal Tubules

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

## Glomeruli

- $\beta$ -2-microglobulin
- Podocin

<http://www.uic.edu/classes/bios/bios100/lecturesf04am/kidney01a.jpg>

# 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

**Academia**

**Advisors**

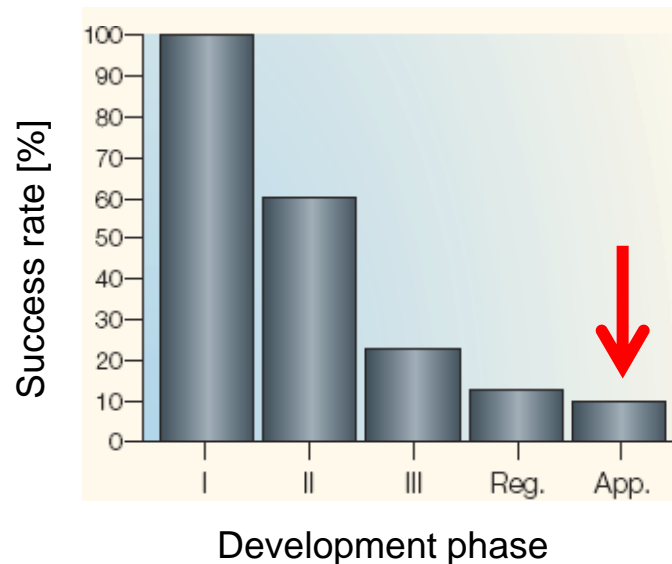
**SMEs**

**EFPIA**

**Collaborators**

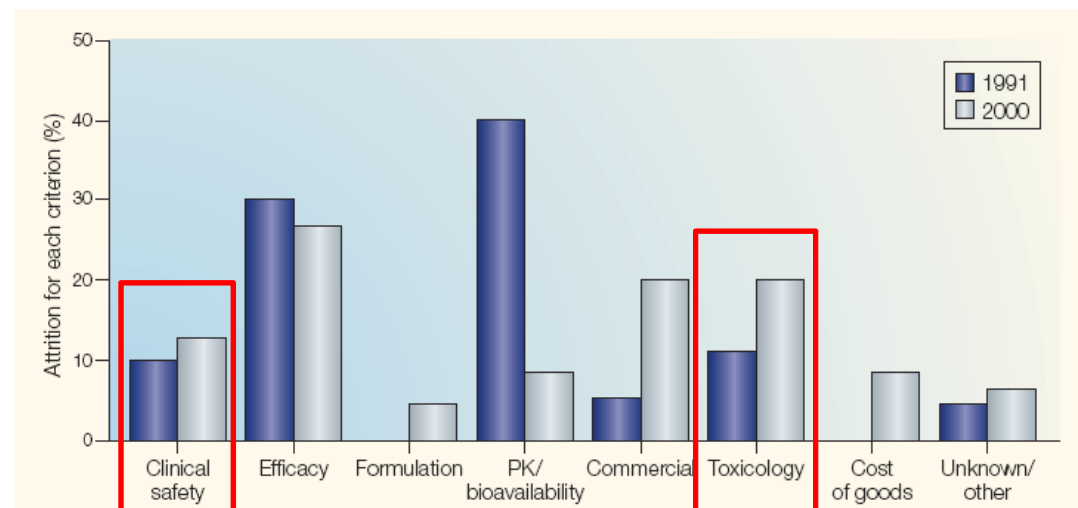
# Drug safety: room for improvement

## The economic perspective



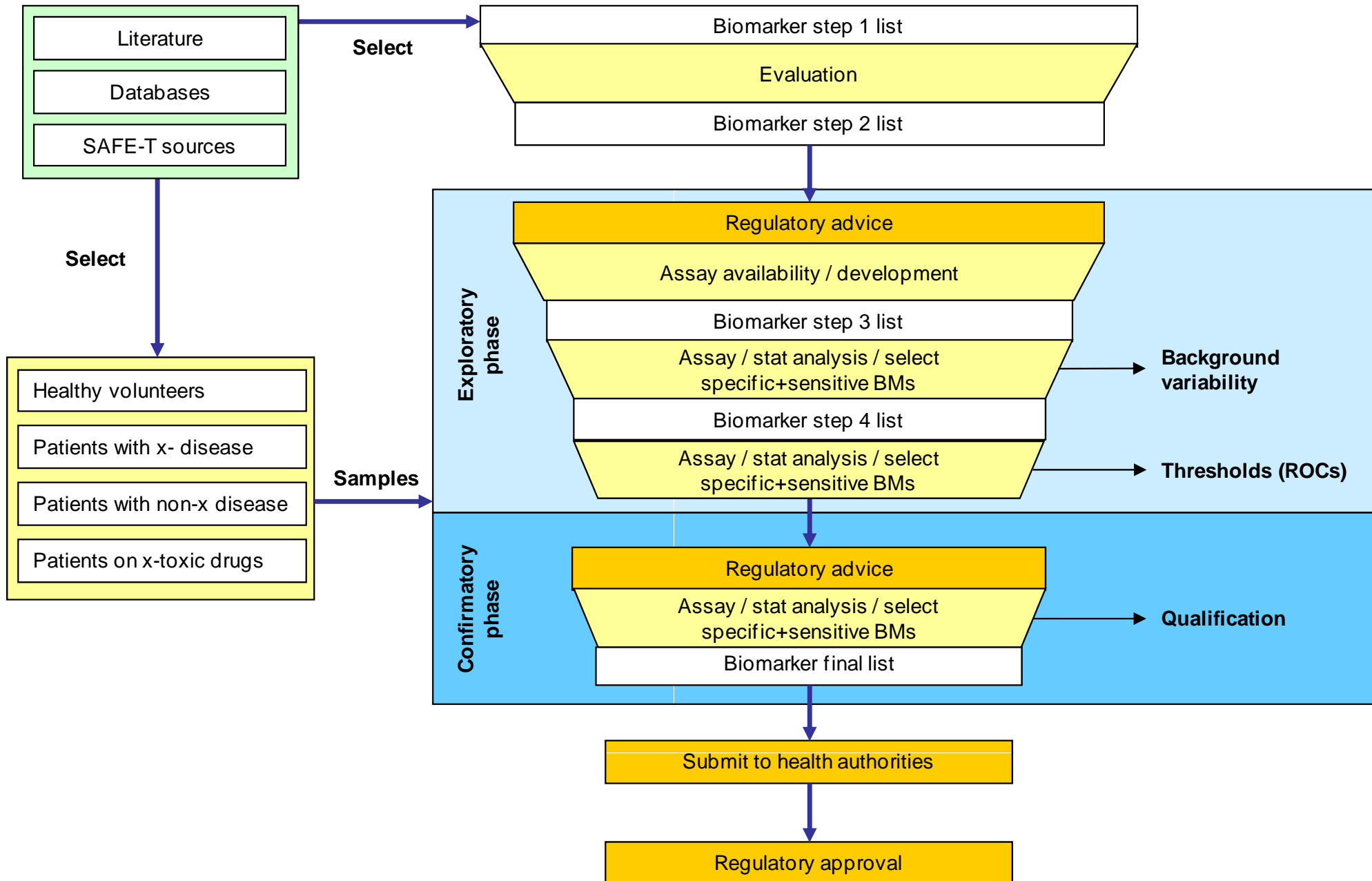
- Around 90% of compounds entering clinical development fail

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





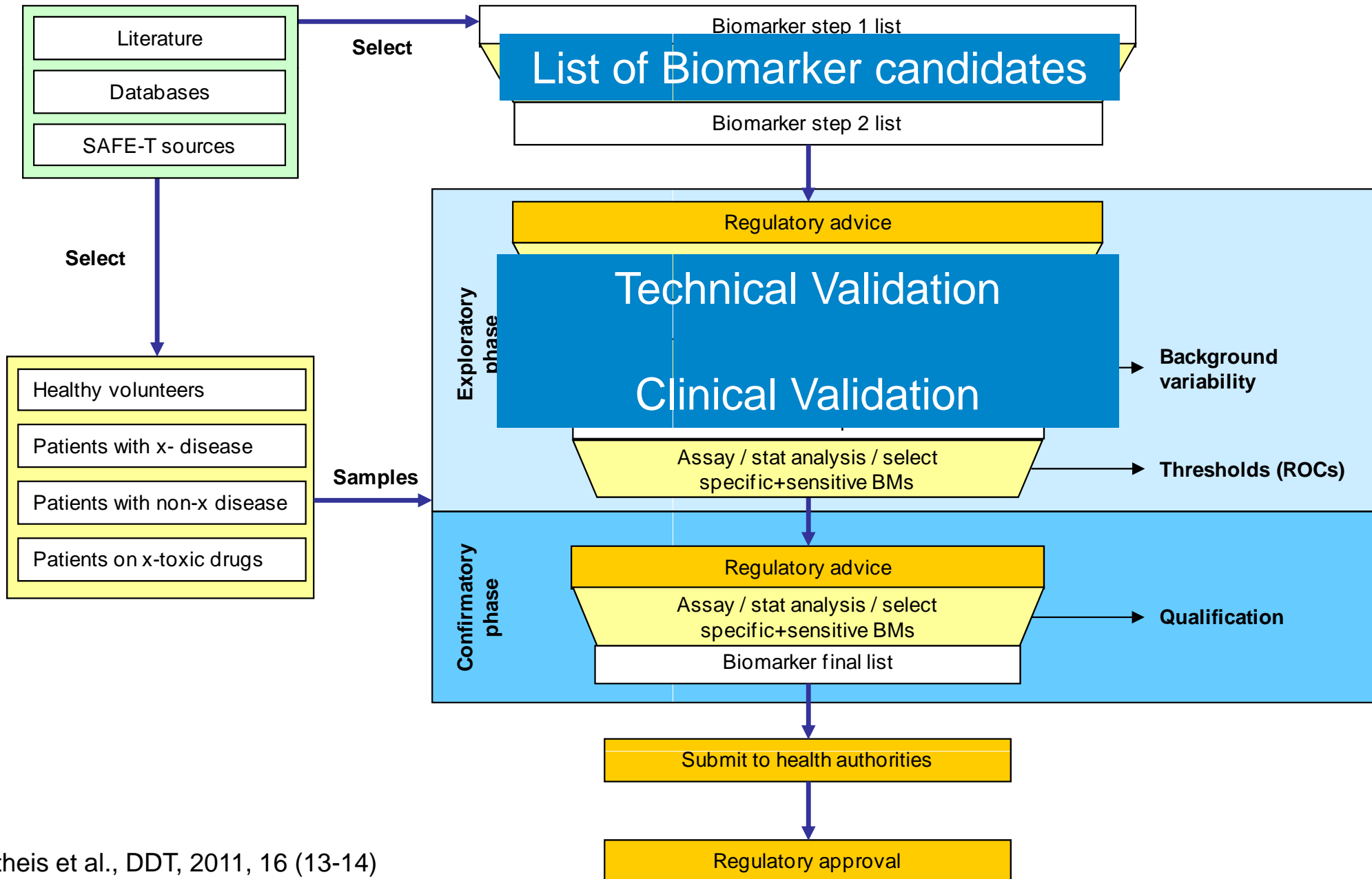
# The Innovative Medicine Initiative The SAFE-T project:





# The Innovative Medicine Initiative

## The SAFE-T project:



# DILI biomarker candidates selected for qualification



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

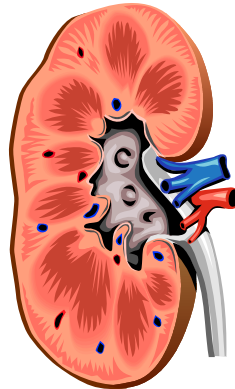
Serum or Plasma Marker	Assays	Liver specificity	Human data	Pathology
miRNA 122	RNA / QPCR	highly specific	yes	hepatocellular damage
albumin mRNA		highly specific	yes	hepatocellular damage
Microglobulin precursor (Ambp) mRNA		highly specific	yes	hepatocellular damage
High mobility group box 1 (acetylated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

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

# SAFE-T

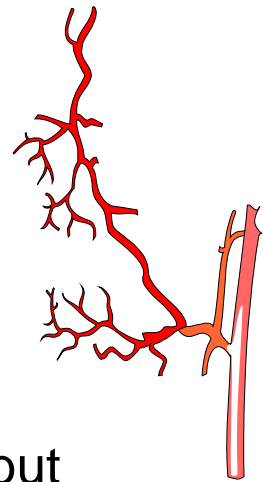
## ■ DIKI

- 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.