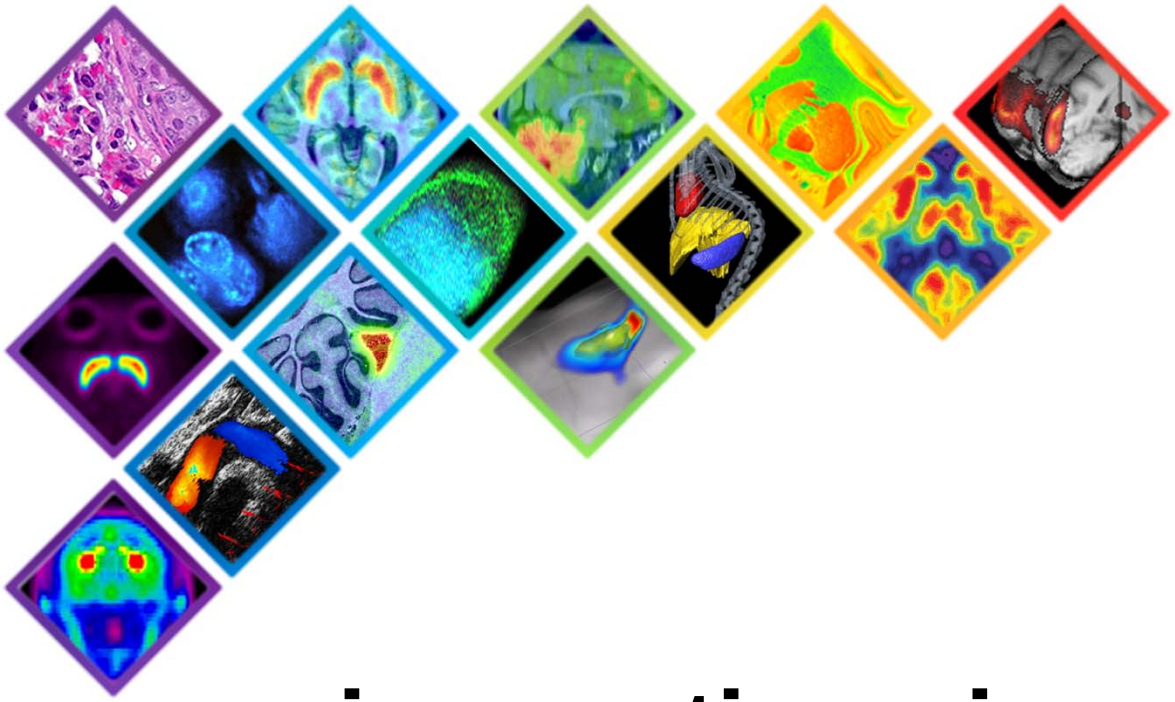

innovations in workflows

P. David Mozley, MD

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objectives

- to describe new workflows for implementing volumetric image analysis
- to acknowledge the costs, challenges, and limitations of these new workflows
- to outline our future steps

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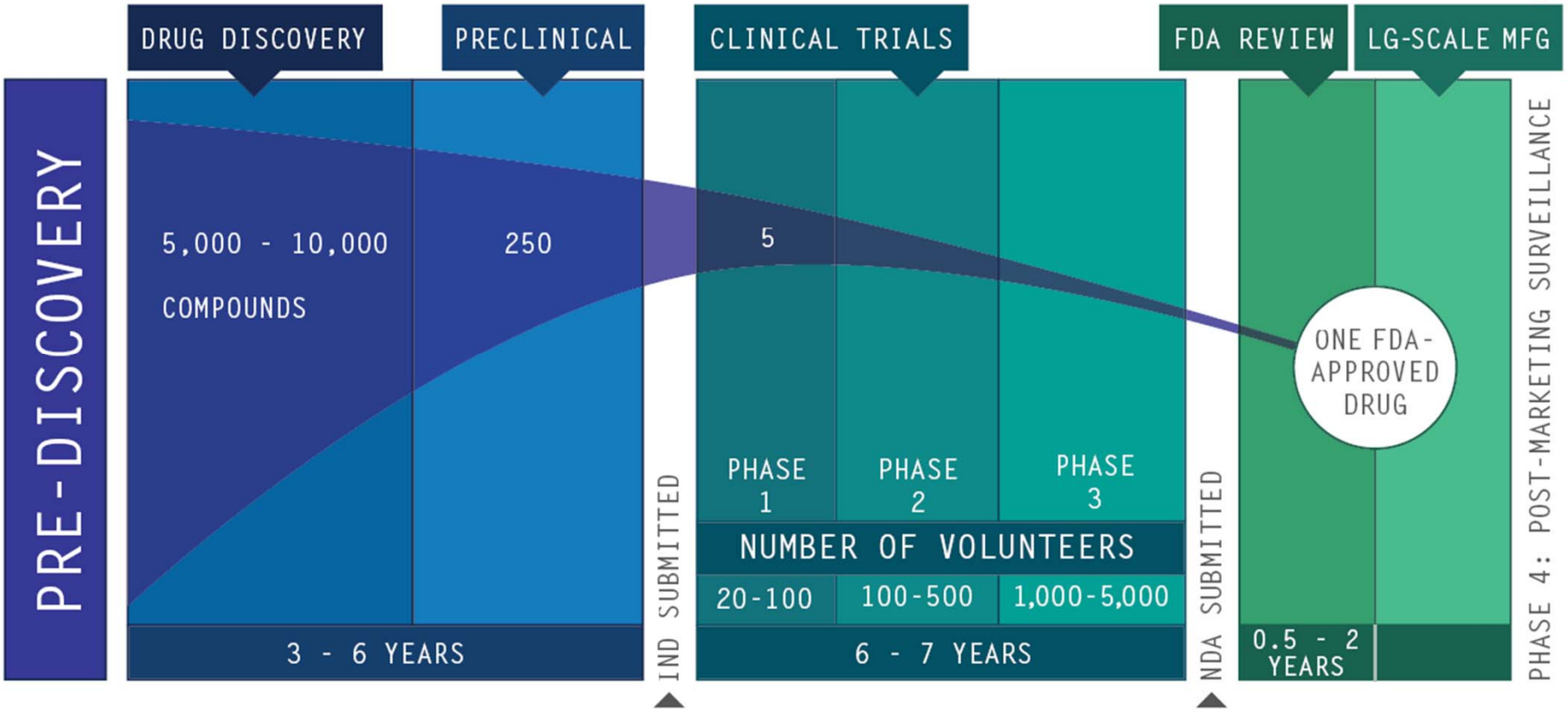
Problem Statement: General



estimated costs $0.8 – 1.7BB

www.inovation.org

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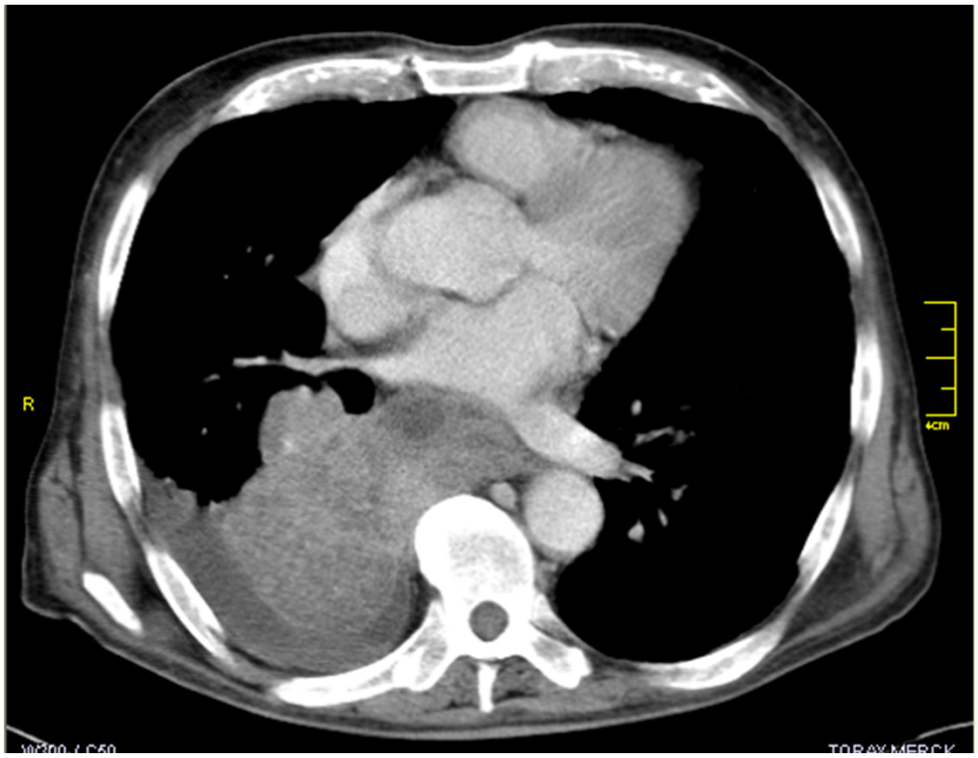
Problem Statement: Specific

- paucity of evidence that quantification adds value



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hypothesis

- better quantification techniques will add value
  - improve patient care
  - decrease number of subjects per trial
  - shorten time-on-study per subject
  - reduce development times
  - speed delivery of new treatments
- problem: too much time, trouble, & treasure

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current state of SOPs

- site investigators measure LD
  - selection of 5 target lesions max
  - make major medical decisions in real time
- backtrack
  - transfer images to central analysis lab
  - lab make new sets of measurements
- problems
  - discordance
  - right-censoring

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old workflow

- first run standard RECIST drill
- then selection of target lesions for volume measurement by radiologists
- semi-automatic edge detection algorithm
- manual revision of edges
- certification of final boundaries
- automatic computation
  - 3D tumor volume [mm^3]
  - 1D longest diameter ≡ greatest distance [mm] between any two in-plane pixels on any slice in the stack of tomographic images representing the target

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new workflow: stage 1

- WAS:
  - selection of 5 target lesions by radiologists
- NEW:
  - measurement of all tumors by trained technologists
  - then certification of status by radiologists
    - confirm appropriate selection of target lesions, else delete
    - confirm boundaries are correct, else revise

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consequences of stage 1 changes

- minimizes selection bias
- maximizes sampling
- more efficient division of labor
- reduces total workflow time
  - "click & grow" is often faster than manual calipers
  - expert review is no longer rate limiting
  - decreases time & costs of expert review

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consequences of stage 1 changes

- measuring whole tumor volume first allows automatic generation of uni-dimensional LDs and WHO cross products
  - “auto-LDs” are already acknowledged as the ideal future state for measuring LDs
  - cross products are still the standard in lymphomas
- thus comparisons are “free of charge”

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problems not solved

- site versus central discordance
- right-censoring

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workflow innovation: stage 2

- deploy a single, free standing image analysis tool at sites
- design specifications include
  - rigidly constrained, guided workflow
  - quantitative assessment tools
  - database of quantitative lesion measurements
  - electronic case report form

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workflow details: stage 2

- image acquisition as per QIBA proffered UPICT
- standard diagnostic reads as per local SOP
  - depend on site radiologists to detect new lesions
  - collaborate on assessment of non-target lesions
- image transfer to laptop
  - any method allowed, e.g., CD, ftp, etc.

workflow details: stage 2

- select target lesions that are either obvious or have been identified by a local expert
  - can be based on verbal descriptions in the standard radiology report or face-to-face collaboration with local radiologists

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target lesion measurements

- "smart read" strategy
  - start at time of first follow up scan
  - if only baseline scans, and no follow up scans, then don't bother
  - if new lesions emerge, then volume measurements at that time-point are obviated
  - if progression of non-target lesions seems unequivocal, then volume measurements are not necessary

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target lesion measurements

- “one click” on a target lesion allows the software to automatically place boundaries on all slices in the 3D stack and extract measurements
- then scrolling through the stack of images allows for deeper understanding AND error checking
  - manually “nudge” & “cut” as indicated, but
  - over-analyzing the images is not encouraged for the sake of reproducibility

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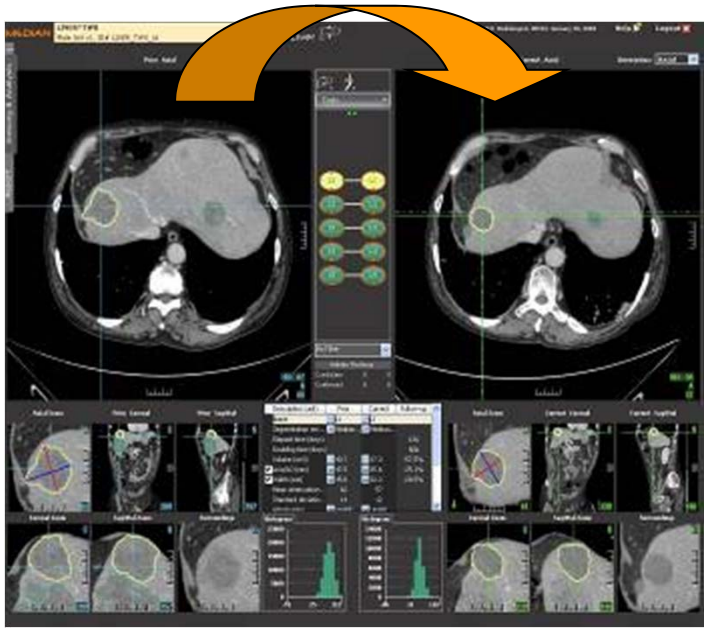
target lesion follow-up

- key feature = constrained workflow
- slice-by-slice check for potential inconsistencies prior to locking

Note: tool automatically positions the viewer on the region of the target lesions on follow up time points



courtesy of Median Technologies, Inc.

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case reports

- automatic reports
- general information about the patient, clinicians and examinations
- snapshots of target lesions
- quantification
  - standard RECIST SOD
  - volumes
  - attenuation…
- detailed results for each confirmed lesion

RECIST Overview

	Target	Non target
Axial LD sum (mm)	**74.1%** 40.8→71.0	**0.0%** 0.0→0.0
Volume sum (cm3)	**259.2%** 2.4→8.5	**0.0%** 0.0→0.0
Number of Lesions (prior)	4	0
Disappeared Lesions	0	0
New Lesions	0	0

expect some failures, like RECIST

- When?
  - tumor morphology becomes overly complex
  - tumor masses becomes highly heterogeneous
  - tumors invade other organs or compartments, e.g., penetrate the diaphragm, chest wall, etc.
- Where?
  - areas of co-morbidity, e.g., pleural effusions, atelectasis, etc.
  - tissues with similar contrast, e.g., bowel wall

coping with failures

- treat masses as non-target lesions
- over classify findings as non-evaluable
- consultation with site radiologists
- practice medicine as per local standard of care

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making treatment decisions

- adverse events: as per SOP
- clinical signs of progression: as per SOP
- new lesions: as per SOP (rely on local radiology reads as always)
- non-target / non-measurable disease: as per RECIST 1.1 (unequivocal signs of progression)

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making treatment decisions

- increases in volume:
  - check the boundaries on every slice; look at the longest diameters, cross products, and areas for those slices
  - be conservative; recall that small changes in small masses are often artifacts from differences in image acquisition parameters
  - when in doubt, consider allowing patients to remain on trial one more round

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verification procedures for sites

- i-CRO uses their own experts & image analysis tools to quantify volumes
- Merck Imaging tries to reproduce site results with site software
- Merck compares all results
- feedback loop to sites includes both i-CRO & Merck assessments

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qualification procedures: stage 2

- nothing new: relationships to health outcomes as per SOP

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Conclusions

- new workflow at i-CRO
  - now nearly universal: all phases
  - starting with whole tumor volume is faster, cheaper, better
  - minimizes target lesion selection bias
- new workflow at sites could
  - reduce discordance
  - decrease censoring and thus accelerate trials
  - improve individual patient care

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¿ Questions ?

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