Companion Diagnostics

End-User Perspective

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Uses of biomarkers in oncology

- Diagnosis
- Prognosis
- Predict response
- Predict toxicity
- Predict risk of additional primaries

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A few examples

IHC	DNA (somatic)	DNA (germline)	Imaging
ER/PR	BRAF V600E	CYP2D6	PET response
HER2	HER2 FISH	BRCA1/2	
KIT	ALK fusion		
	EGFR mutation		
	KIT mutation		
	KRAS		

Often incomplete concordance between biomarker and outcome

Clinical validity is biggest clinical issue

Clinical validity ≠ Clinical utility

Looseness of terminology is not helpful

Stakeholder suggestions

- "Developers should offer proof of clinical utility"
- "CLIA role should be strengthened to assure clinical validity"

Challenges

- No consensus as to what metrics establish "sufficient" clinical validity (association with outcome) or clinical utility (improvement of outcome)

- Optimal trial designs remain undefined
  - Requiring RCT may set too high a bar
  - Designing statistically robust (and ethical) studies difficult
  - Study population of an RCT may not reflect clinical reality

Challenges

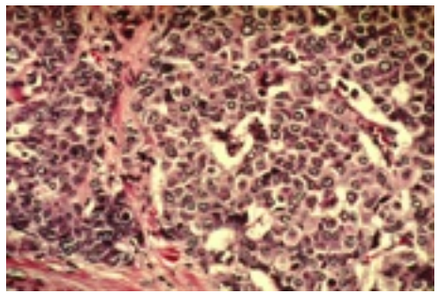
- Sample requirements
- Admixture with normal tissue
- Tumor heterogeneity
- Evolution from primary to metastasis

Regulatory structure has to anticipate the future

Current Model

PATIENT PRESENTS

CLINICIAN CONSIDERS OPTIONS

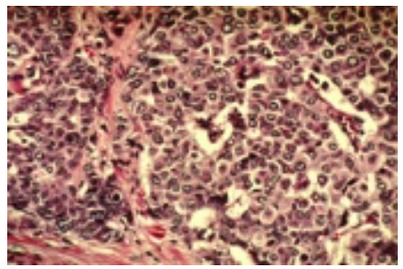


CD test

Treat

Evolving Model

PATIENT PRESENTS



Tumor profiling

CLINICIAN CONSIDERS RESULTS

Treat

New challenges

- For nucleic acid-based diagnostics, single platform replaces mutation-specific tests
    - Partly addressed by CAP suggestion to "define relevant analyte rather than test", recognizing that different technologies vary in performance

- Leaves one needing a general method to delineate which sequence changes are predictive of response
    - Not feasible to validate all potentially significant variants
    - In silico methods to predict functional significance may be sufficient in certain situations, but not always transparent
    - But, may be application-specific (e.g. ivacaftor in CF as opposed to PARPi in gBRCA breast cancer)

Conclusions

- From a clinician's standpoint, major challenge is delineating clinical validity/utility of companion diagnostic in a way that informs clinical decision making in real-world circumstances
- Some proposed stakeholder solutions relate to this challenge without really solving it
- Technologic advances in sequencing may require development of a flexible, more agnostic approach, at least in oncology