Report of assays for monitoring disease status

Performance Evaluation of Molecular Diagnostics in Cancer Treatment

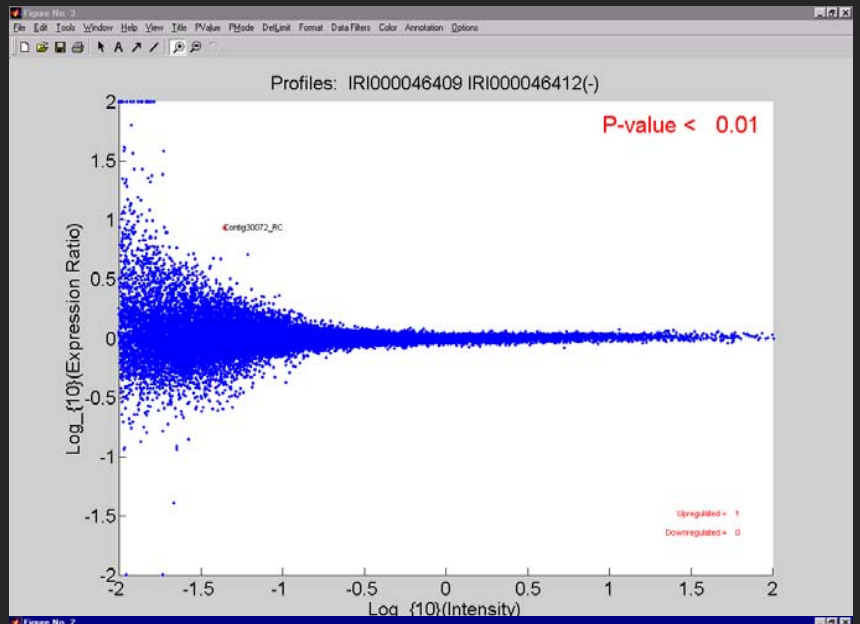
- Intended Use & Indications for Use
- Pre-Market Review of IVDs
  - Analytic and clinical validation
- Independent Validation
- Analytical Validation Steps
- Monitoring
- Clinical Study Design
  - RCT, Enrichment designs

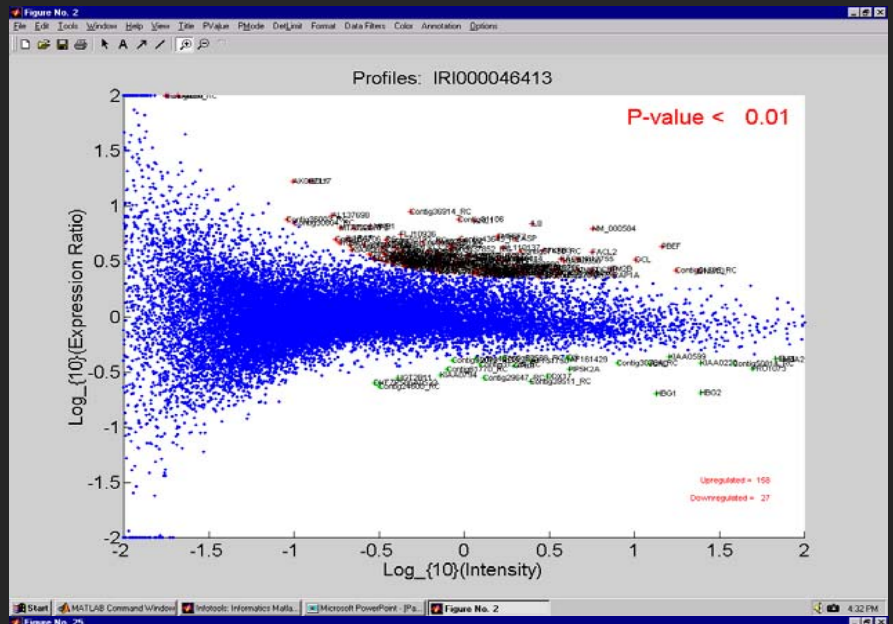
Monitoring

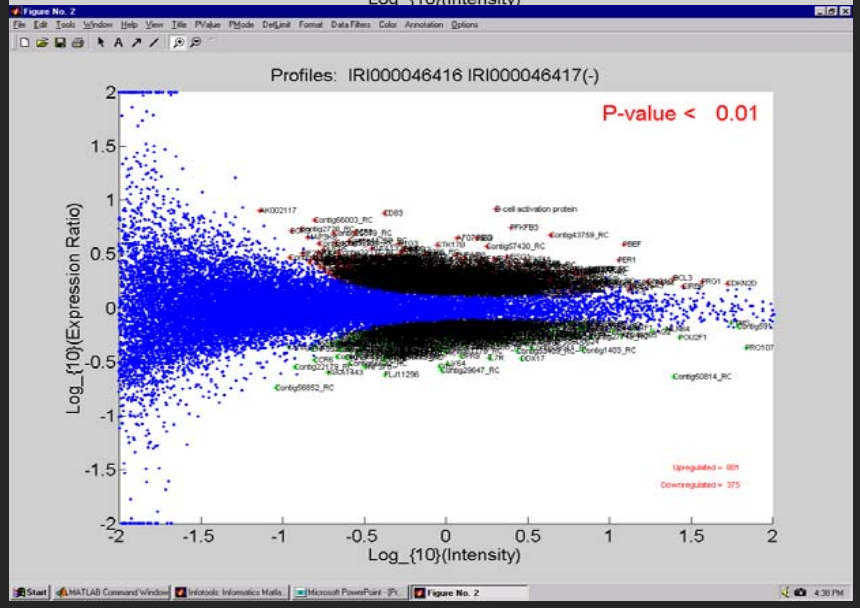
- Change in serial results could be due to
  - Pre-analytical variation (specimen handling, processing, and preparation)
  - Analytical variation (assay variation in results on replicates)
  - Biological heterogeneity (sample to sample)
  - Normal biological variation not of clinical interest

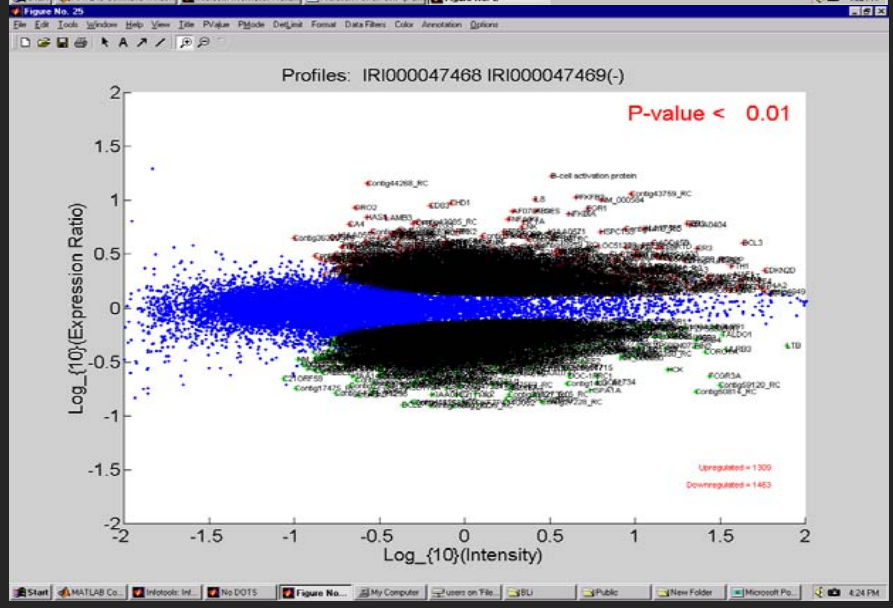
Fraser, C.G., Hyltoff Petersen, P., Lytken Larsen, M. (1990) Clin. Chem. 36/9, 1625-1628, "Setting analytical goals for random analytical error in specific clinical monitoring situations

Gene expression over time



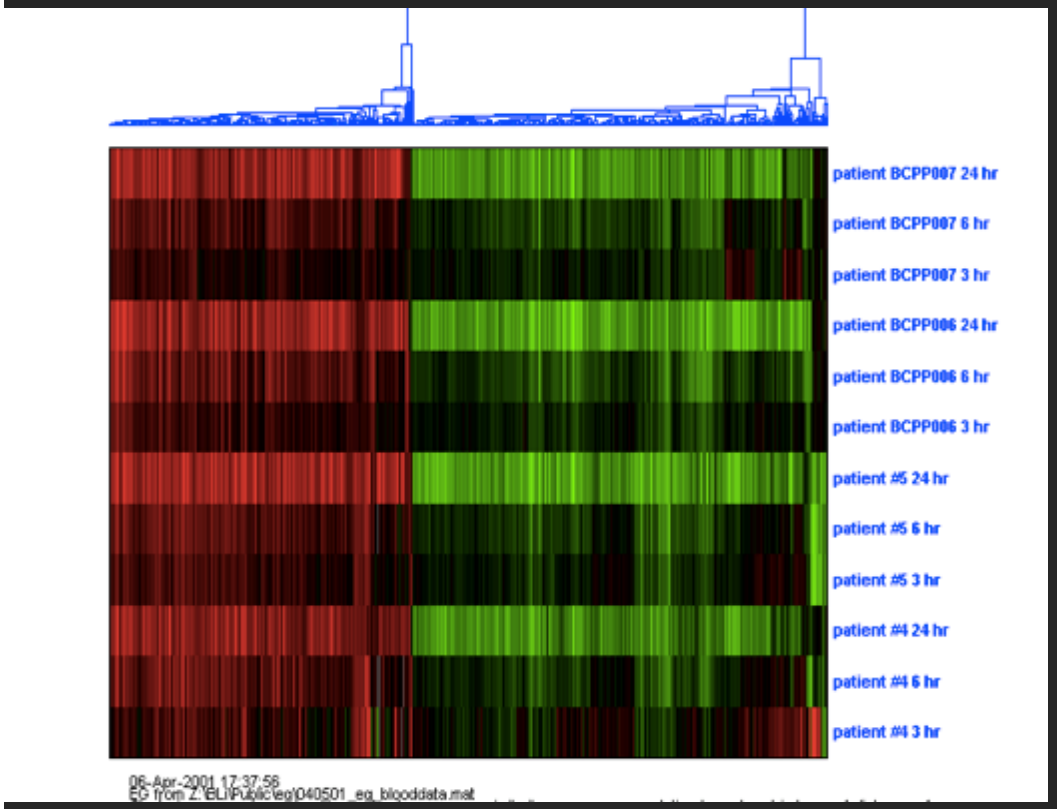


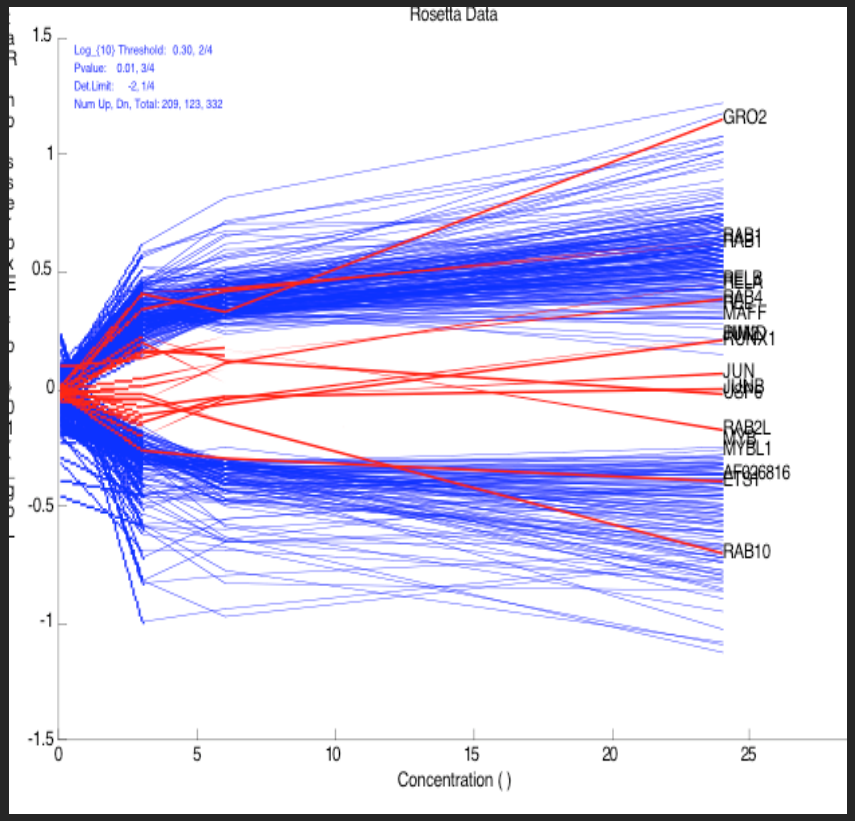




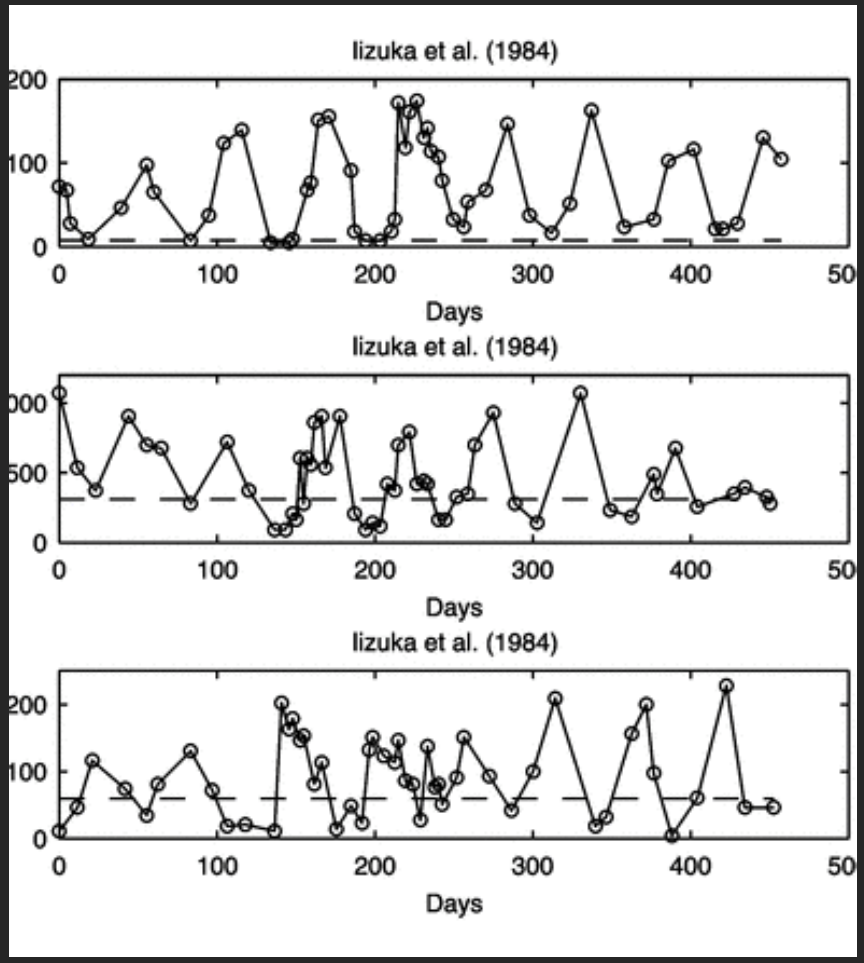
Gene expression over time

4 individuals (3, 6, 24 hr)





Oscillations in CML



we dealt with (3). First, we rewrite (11) in a similar form:

$$\frac{dS}{dt} = b_S\big[S_1 h(S_1,\Theta_1) - S h(S,\Theta)\big] + \varepsilon\big[\lambda_S S_1 h(S_1,\Theta_1) - S\big],$$
$$\alpha\frac{dA}{dt} = b_A\big[A_\alpha h(A_\alpha,\Theta_\alpha) - A h(A,\Theta)\big] + \varepsilon\alpha d_A\big[\lambda_A A_\alpha h(A_\alpha,\Theta_\alpha) - A\big]. \tag{15}$$

Next, we assume that S and A are slowly varying on a time scale of $O(1/\varepsilon) \gg 1$; expanding the delayed terms, we have

$$S_1 \approx S - \dot{S} + \cdots, \qquad A_\alpha \approx A - \alpha\dot{A} + \cdots,$$
$$\Theta_1 \approx \Theta - \dot{\Theta} + \cdots, \qquad \Theta_\alpha \approx \Theta - \alpha\dot{\Theta} + \cdots, \tag{16}$$

and thus, defining the slow time

$$\tau = \varepsilon t, \tag{17}$$

we derive the slowly varying approximation for S and A,

$$M\begin{pmatrix} S' \\ A' \end{pmatrix} = \begin{pmatrix} \{\lambda_S h(S,\Theta) - 1\}S \\ d_A\{\lambda_A h(A,\Theta) - 1\}A \end{pmatrix} \tag{18}$$

where $S' = dS/d\tau$, $A' = dA/d\tau$, and the matrix M is given by

$$M = \begin{pmatrix} 1 + b_S H(S,\Theta) & b_S J(S,\Theta) \\ b_A J(A,\Theta) & 1 + b_A H(A,\Theta) \end{pmatrix}, \tag{19}$$

where

$$H(\xi,\Theta) = h + \xi(h_\xi + h_\Theta), \qquad J(\xi,\Theta) = \xi h_\Theta. \tag{20}$$

Inverting this, we have

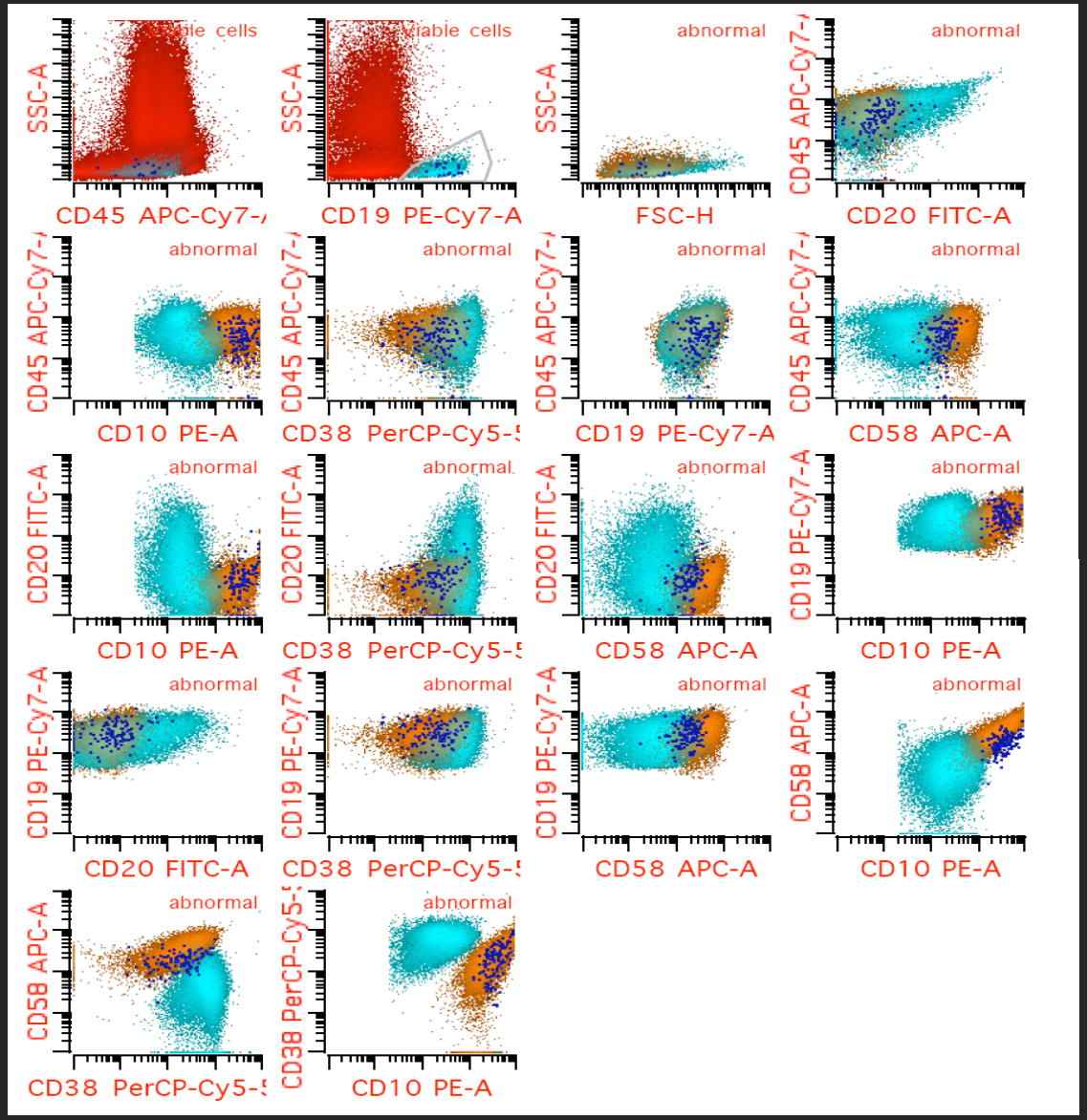
$$\begin{pmatrix} S' \\ A' \end{pmatrix} = \Delta^{-1}\begin{pmatrix} 1 + b_A H(A,\Theta) & -b_S J(S,\Theta) \\ -b_A J(A,\Theta) & 1 + b_S H(S,\Theta) \end{pmatrix}\begin{pmatrix} \{\lambda_S h(S,\Theta) - 1\}S \\ d_A\{\lambda_A h(A,\Theta) - 1\}A \end{pmatrix}, \tag{21}$$

where the determinant of M is given by

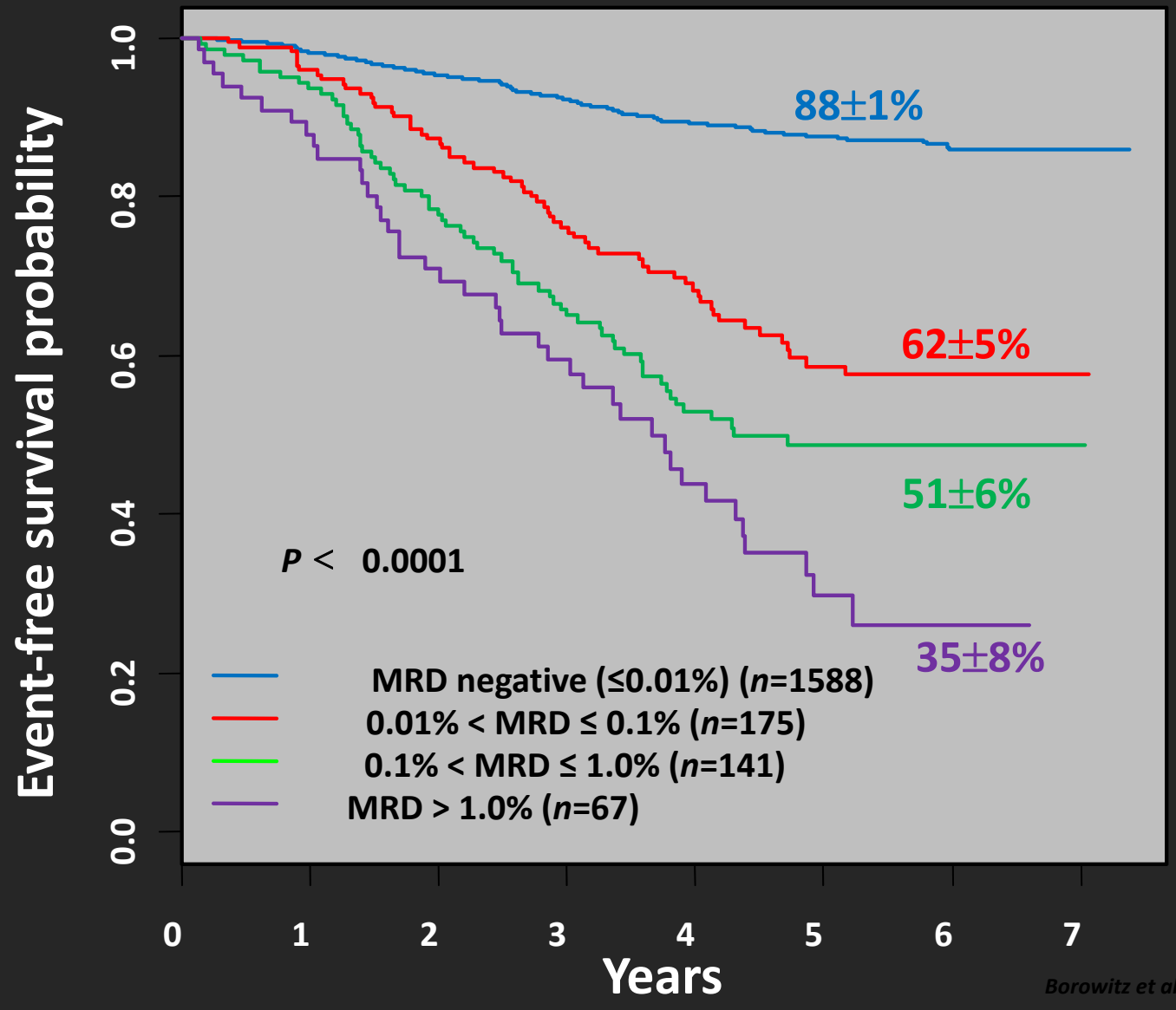
Drobnjak, Bull Math Biol, 2011

Detection of MRD Via Flow Cytometry

Courtesy of Michael Borowitz, MD PhD



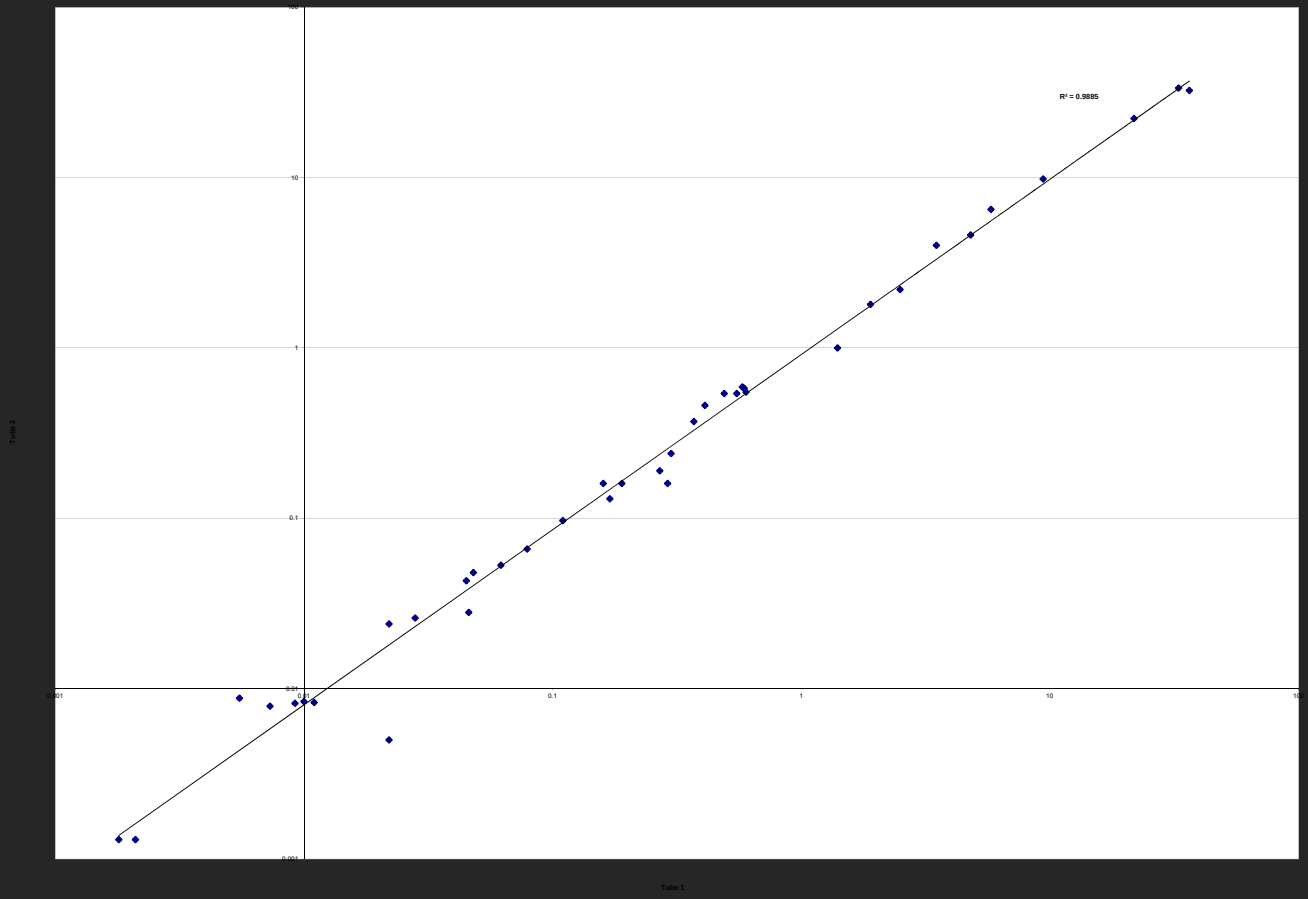
End Induction BM MRD is Highly Prognostic: COG P9900



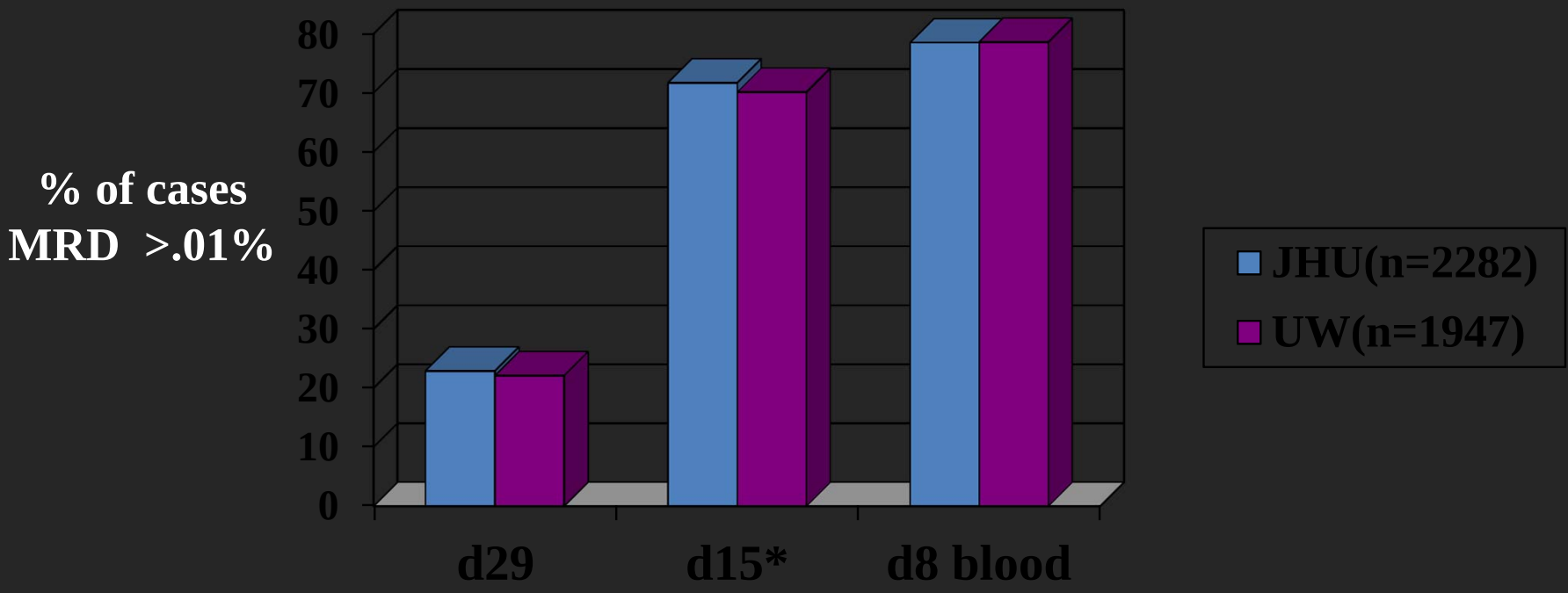
Borowitz et al Blood 111:5477,2008

Reproducibility of Flow MRD

Unpublished data, courtesy of Michael Borowitz



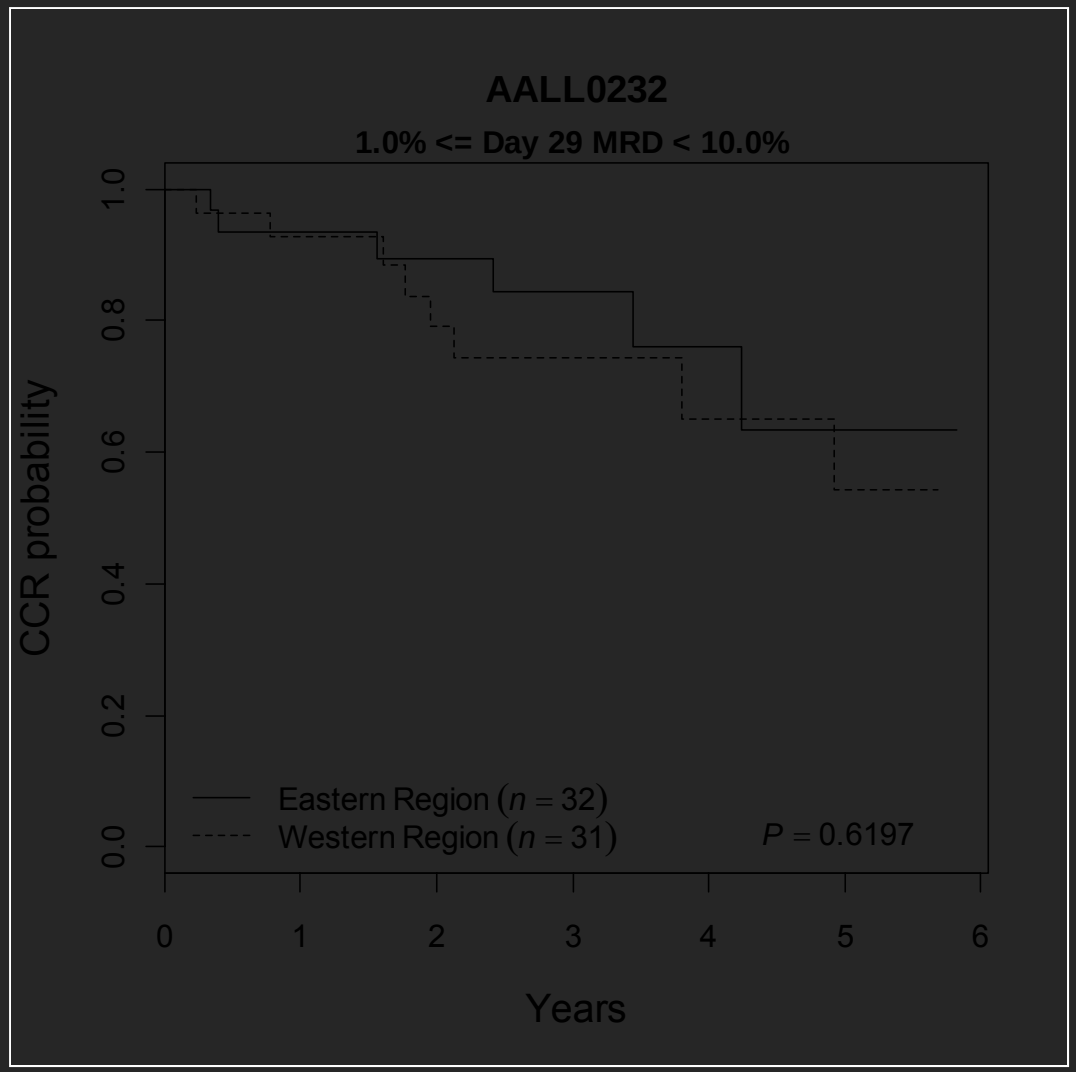
Comparison of Flow MRD in 2 Central Reference Labs: AALL03B1 (n=4232)



* day 8 M1 patients excluded

Unpublished data, Borowitz and Wood

COMPARISON OF OUTCOMES
UW vs JHH MRD >1%

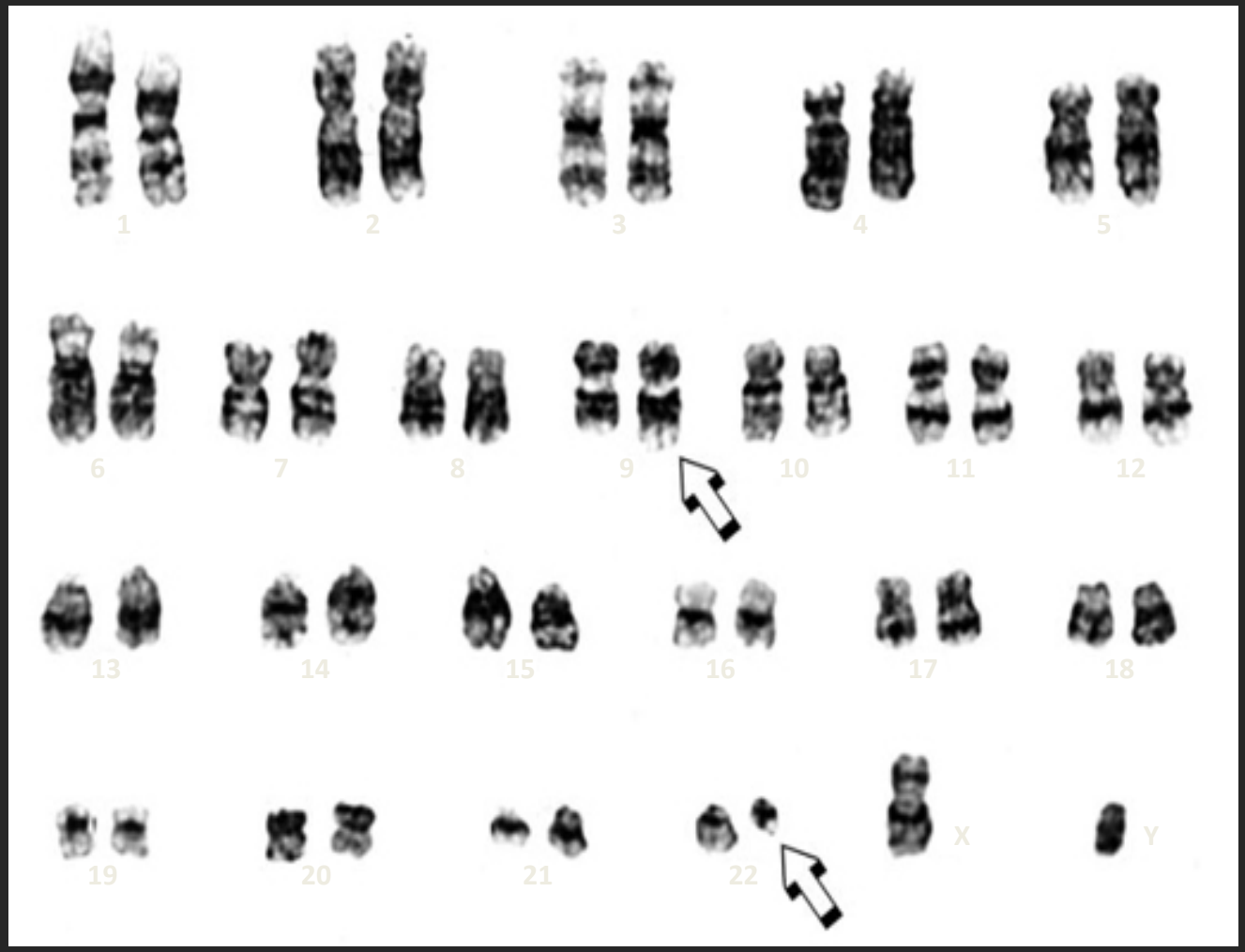


Unpublished data, courtesy Mike Borowitz

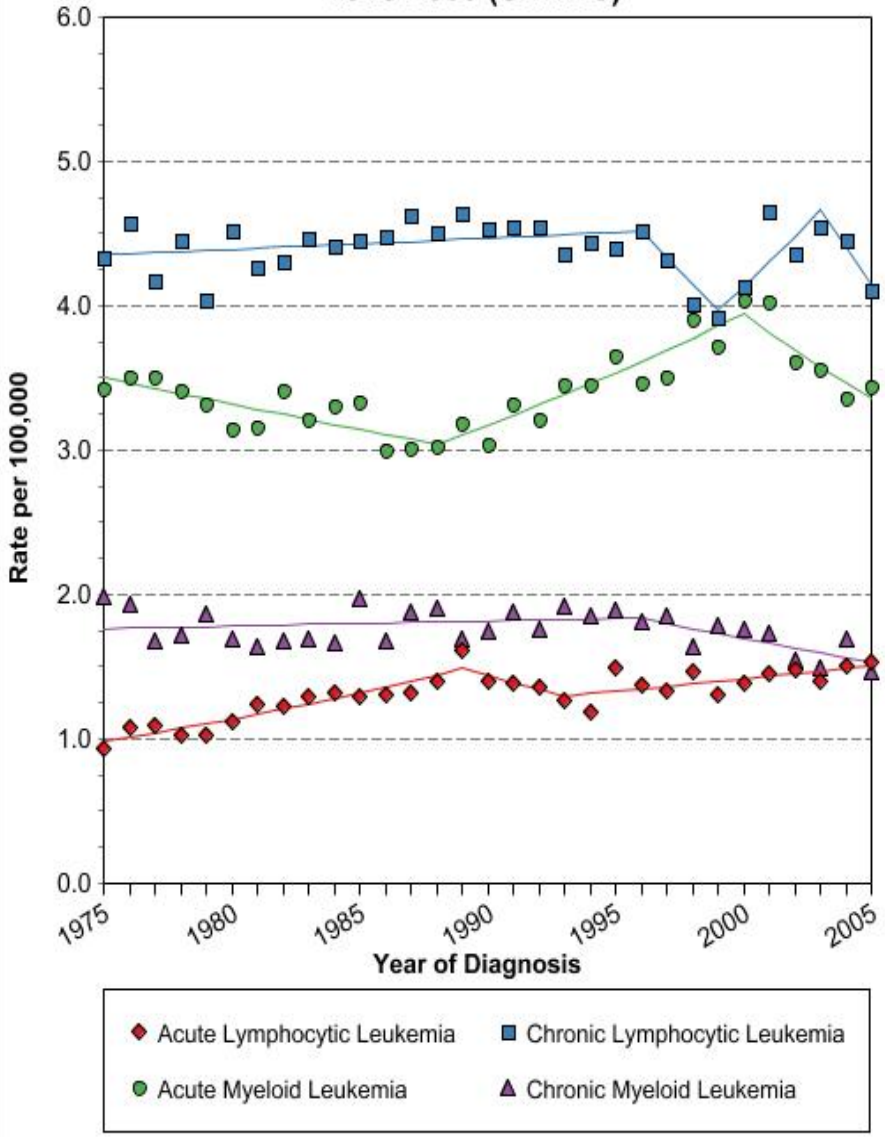
Flow MRD in ALL Conclusions

- End-induction flow MRD is the most powerful prognostic marker in COG ALL trials
  - Used in real time to allocate therapy for >12,000 pts enrolled in COG ALL trials 2004-2012
- Standardization in two central labs using standardized, but not identical methodologies/instruments
- *This can be used to drive therapy and trial design*
- *This is not easily duplicated in other labs*

Cytogenetic Abnormality of CML
The Philadelphia Chromosome

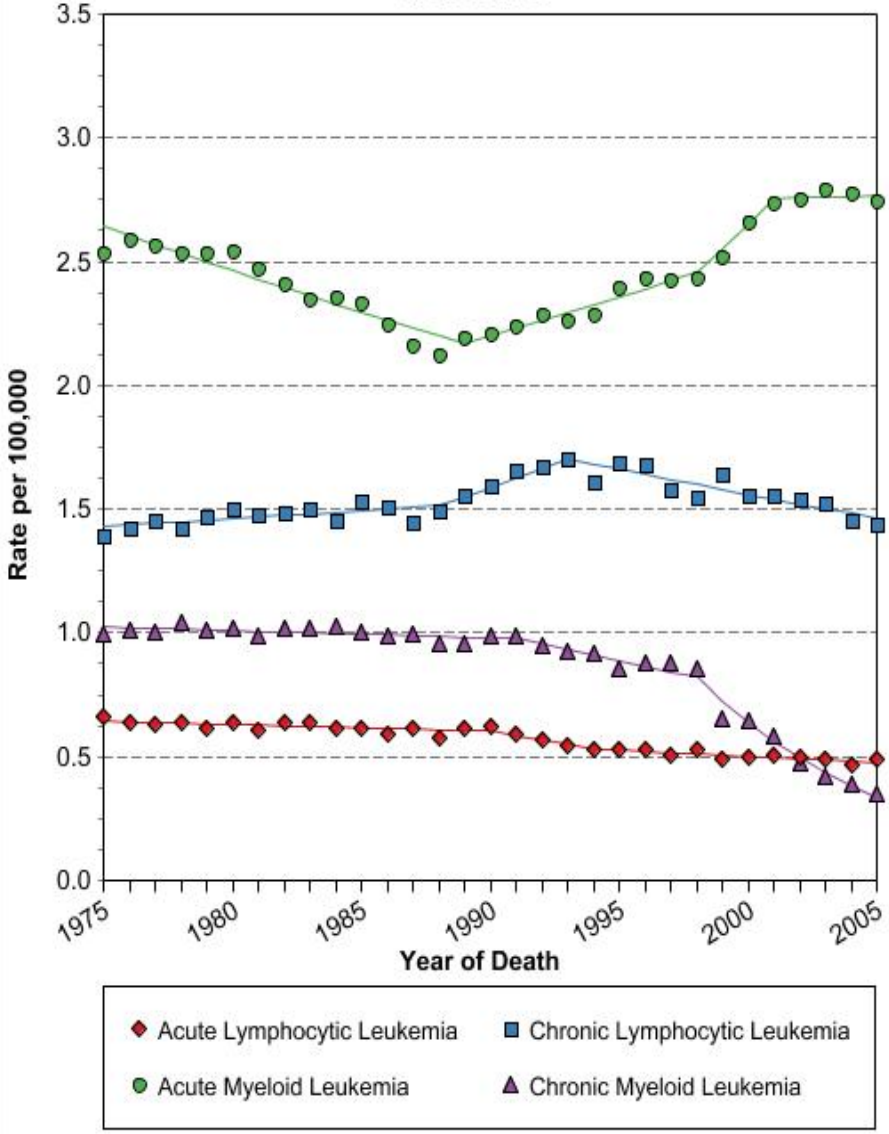


Age-Adjusted SEER Incidence Rates By Cancer Site For All Ages, All Races, Both Sexes 1975-2005 (SEER 9)



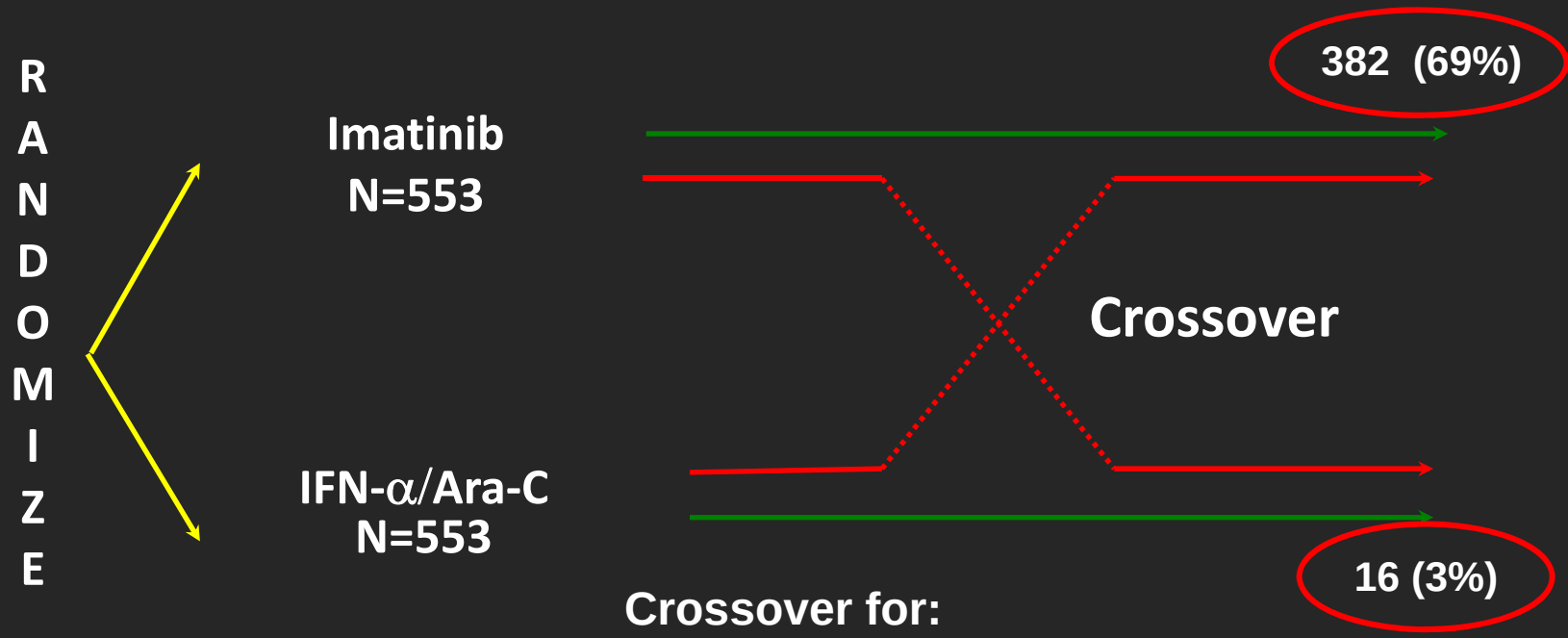
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

Age-Adjusted U.S. Mortality Rates By Cancer Site For All Ages, All Races, Both Sexes 1975-2005



Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

IRIS trial: Newly Dx CP CML



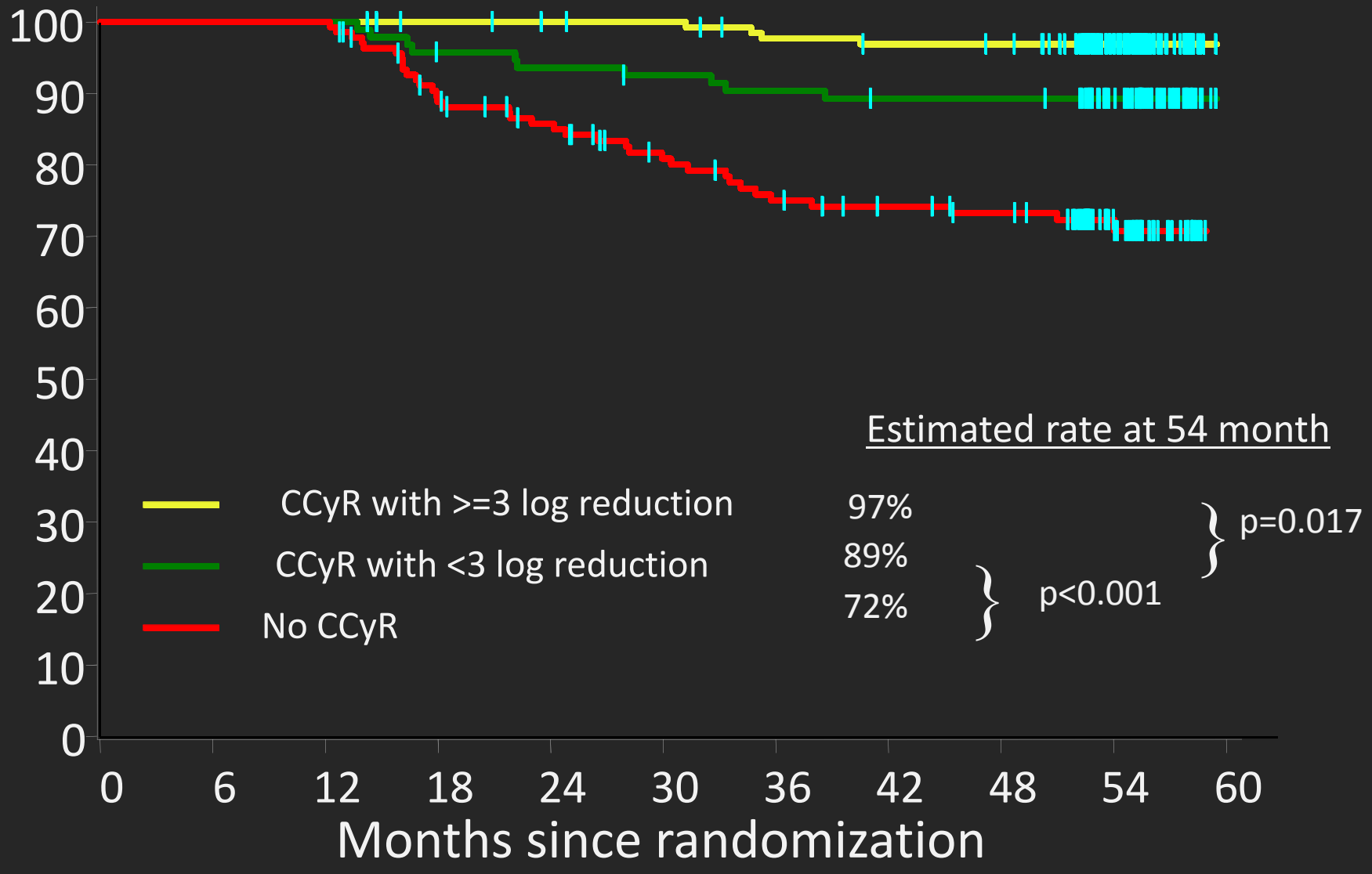
Crossover for:

- Lack of response
- Loss of response
- Intolerance of treatment

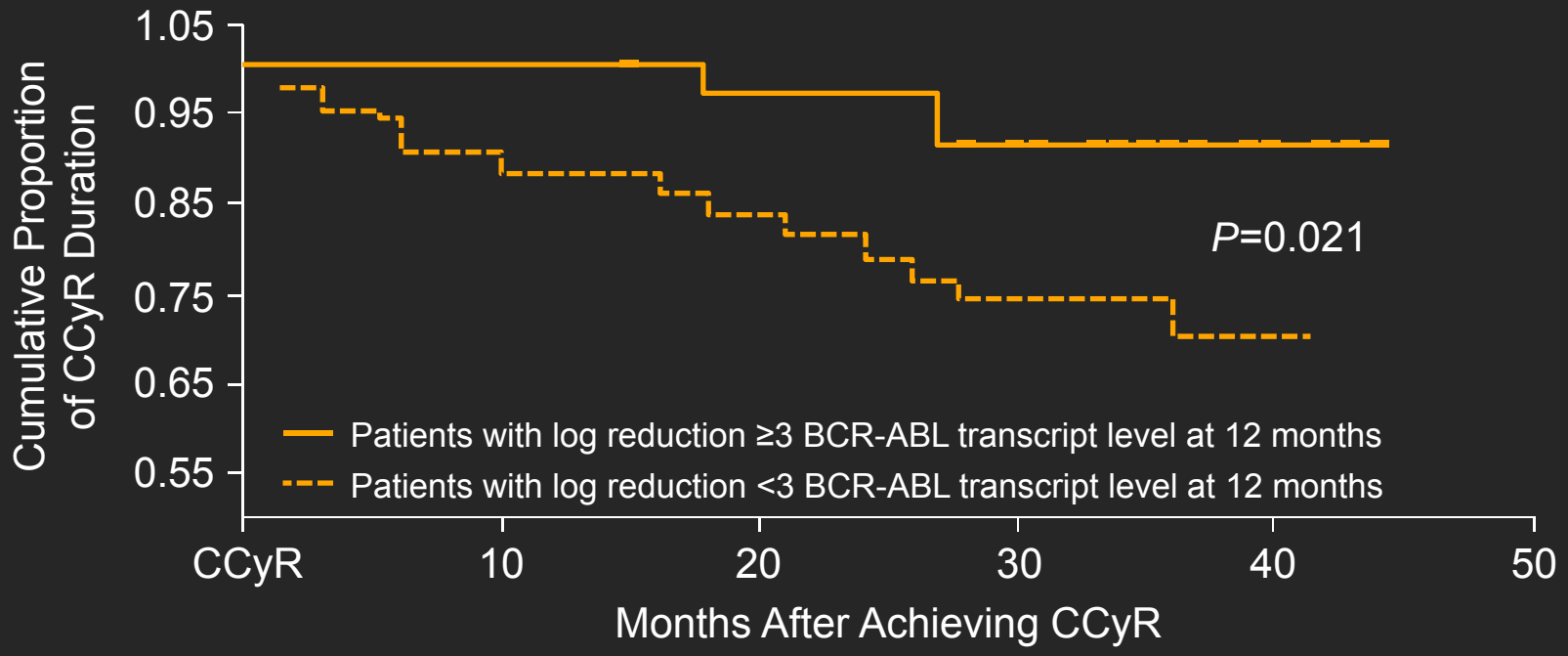
Enrollment period: June 2000 to January 2001

Druker et al. NEJM 2006; 355: 2408-17

Molecular response to imatinib predicts outcome



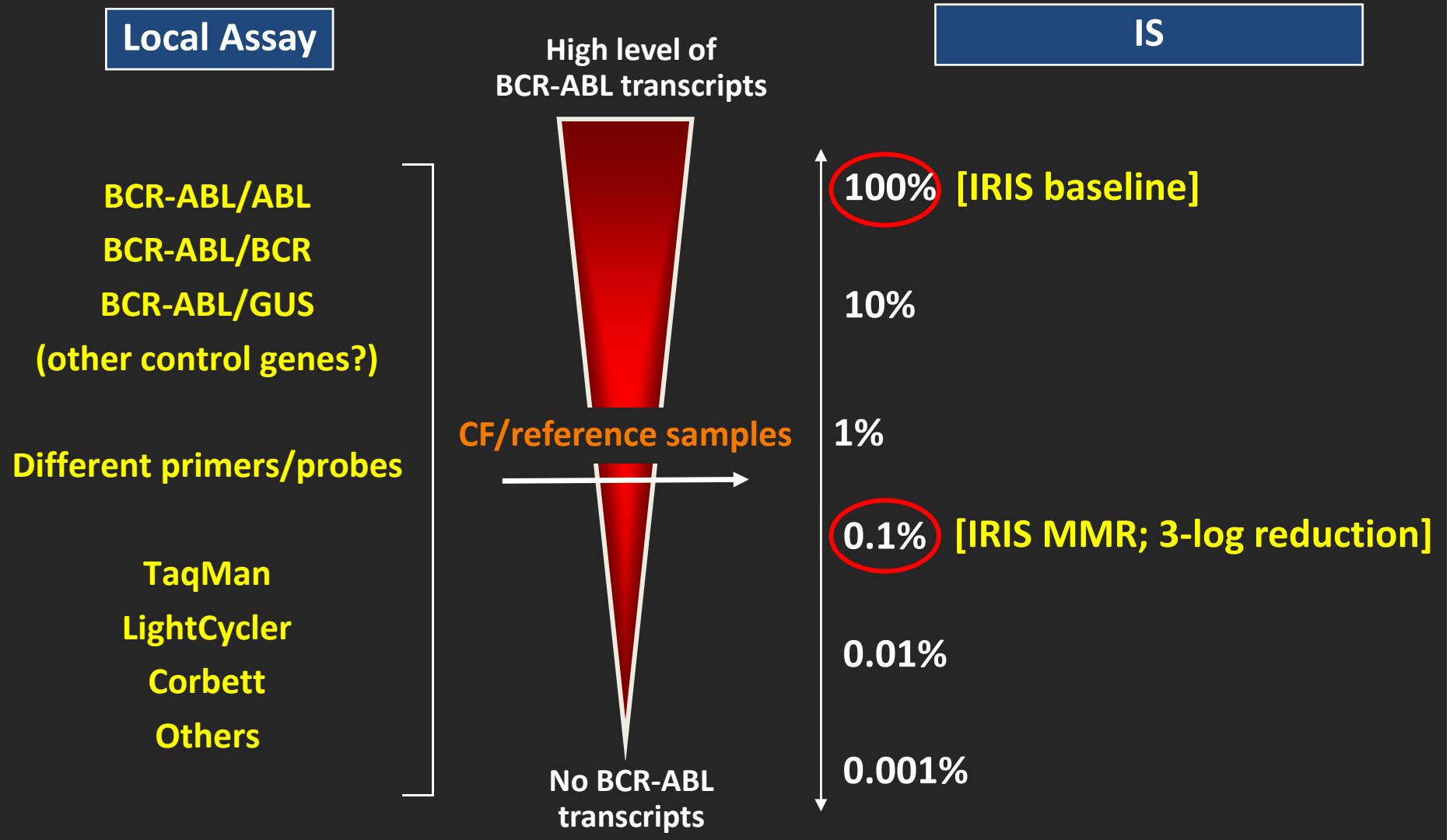
MMR Predicted Duration of CCyR



- Patients who achieved an MMR (≥3-log reduction of BCR-ABL mRNA transcript level from median baseline) at 12 months of imatinib therapy had significantly longer cytogenetic remission durations than those without (*P*=0.021)

Iacobucci I et al. *Clin Cancer Res* 2006;12(10):3037-3042.

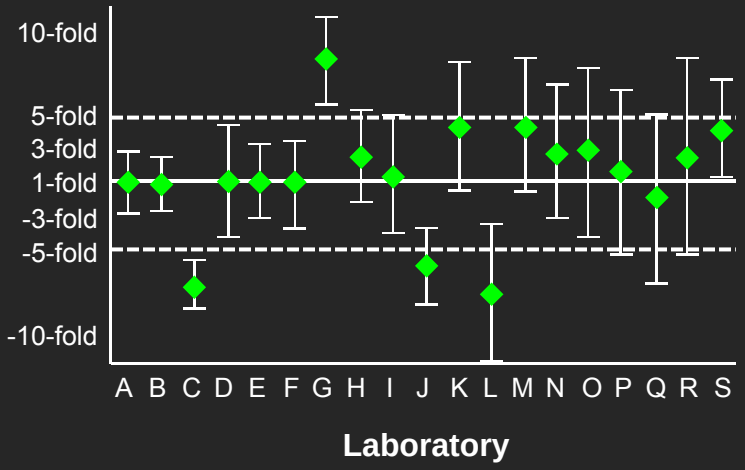
IS Established by IRIS



Hughes T, et al. *Blood*. 2006;108:28-37.

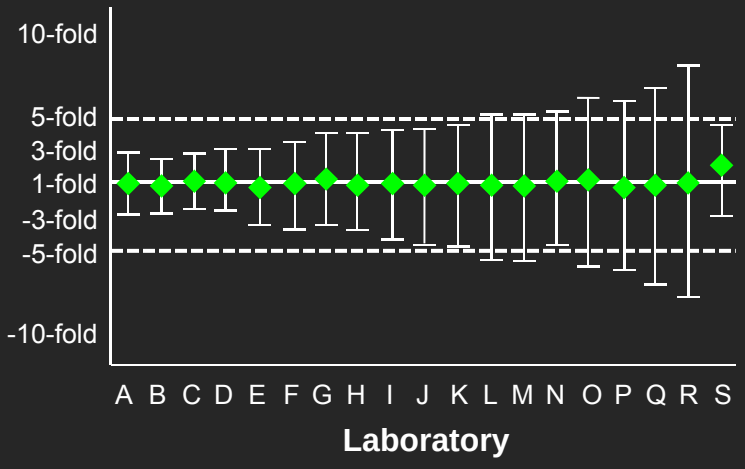
Conversion of RQ-PCR Results to IS Allows Comparison of Results Between Laboratories

Difference From Reference Lab Before IS Conversion



- Laboratories analyzing the same samples arrive at different values[a]

Difference From Reference Lab After IS Conversion



- Conversion to IS makes results from different laboratories comparable

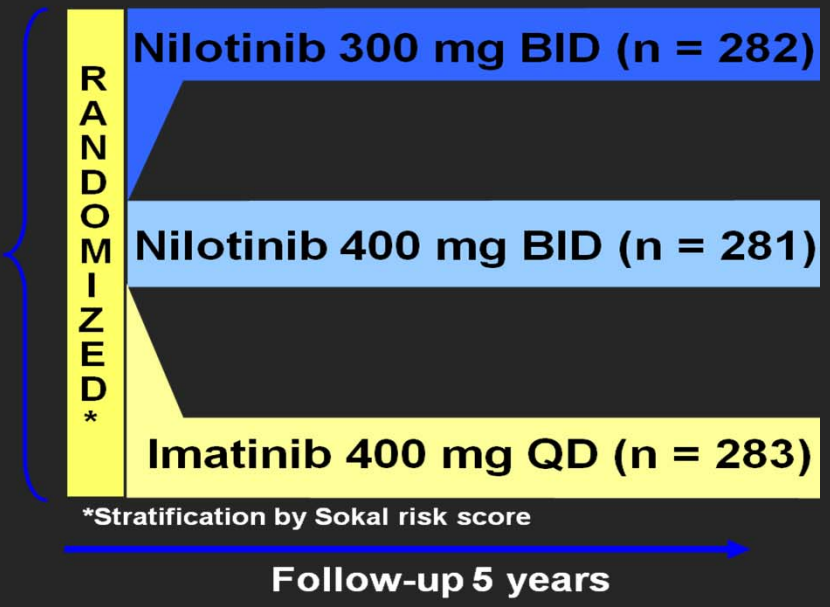
[a]Results differ because of use of different protocols, assays, control genes, standardized baselines.
Branford S et al. *Blood*. 2008;112(8):3330-3338.

2nd Generation TKIs vs Imatinib

Treatment-Naïve CP-CML

ENESTnd

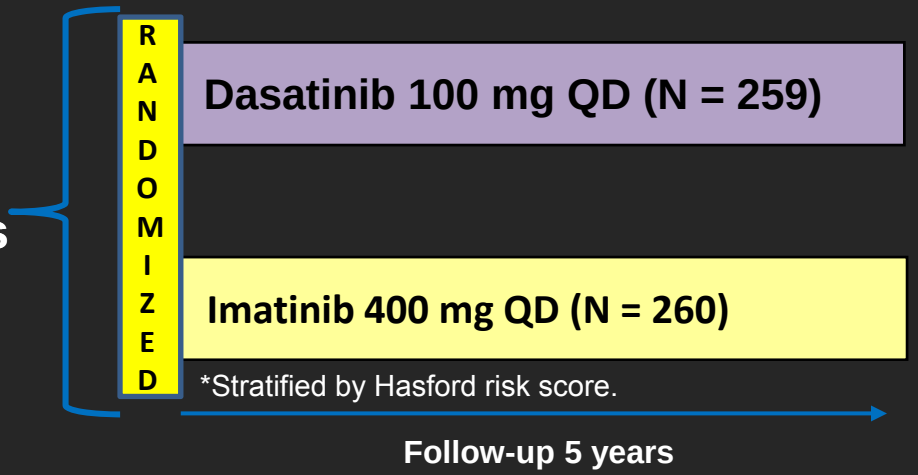
- N = 846
- 217 centers
- 35 countries



Primary end point: MMR at 12 months

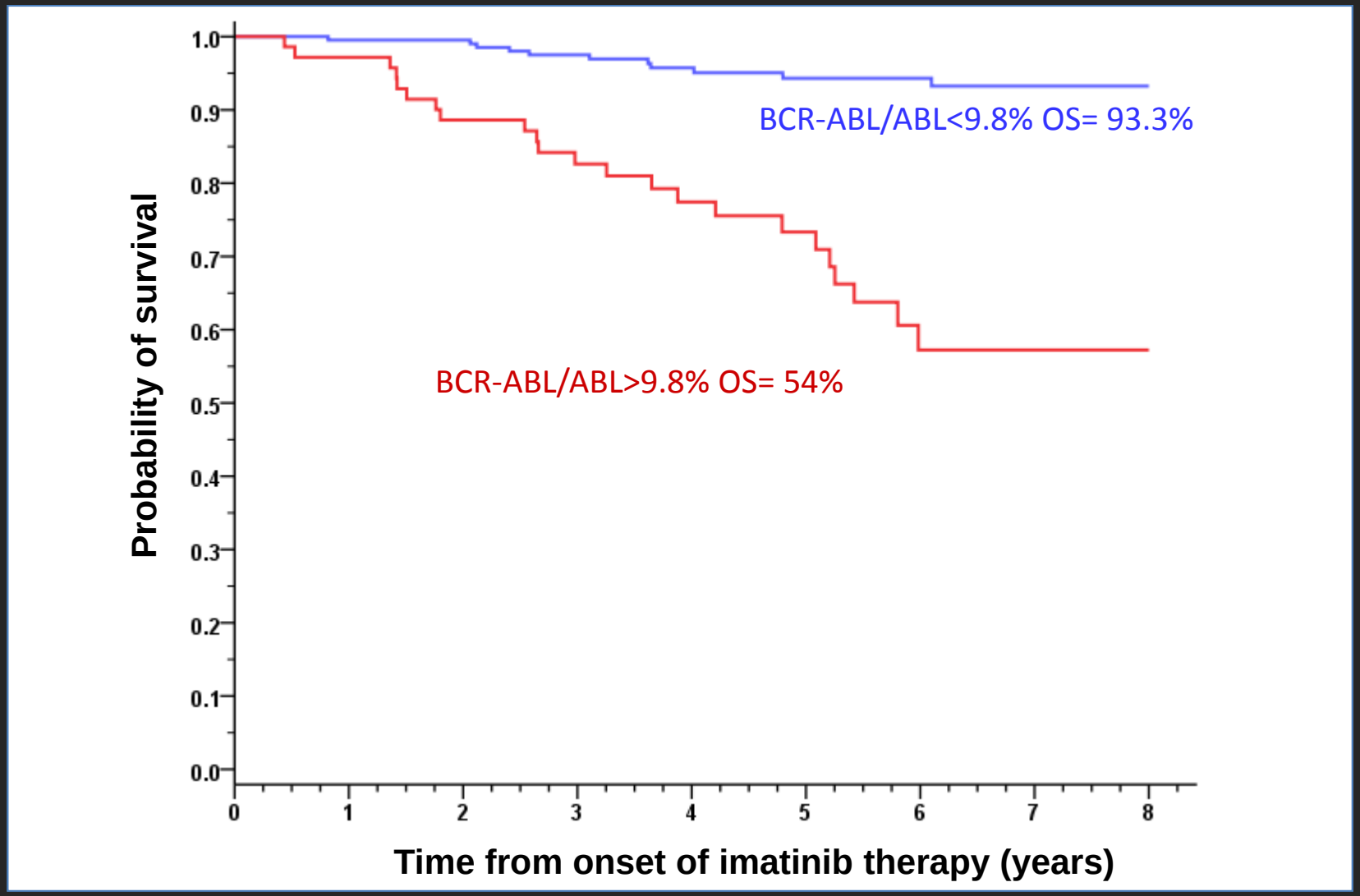
DASISION

- N = 519
- 108 centers
- 26 countries



Primary end point: confirmed CCyR at 12 months

3 month BCR-ABL level and OS: Cut off IS ~10%



Marin et al. J Clin Oncol. 2012 Jan 20;30(3):232-8 (adapted).

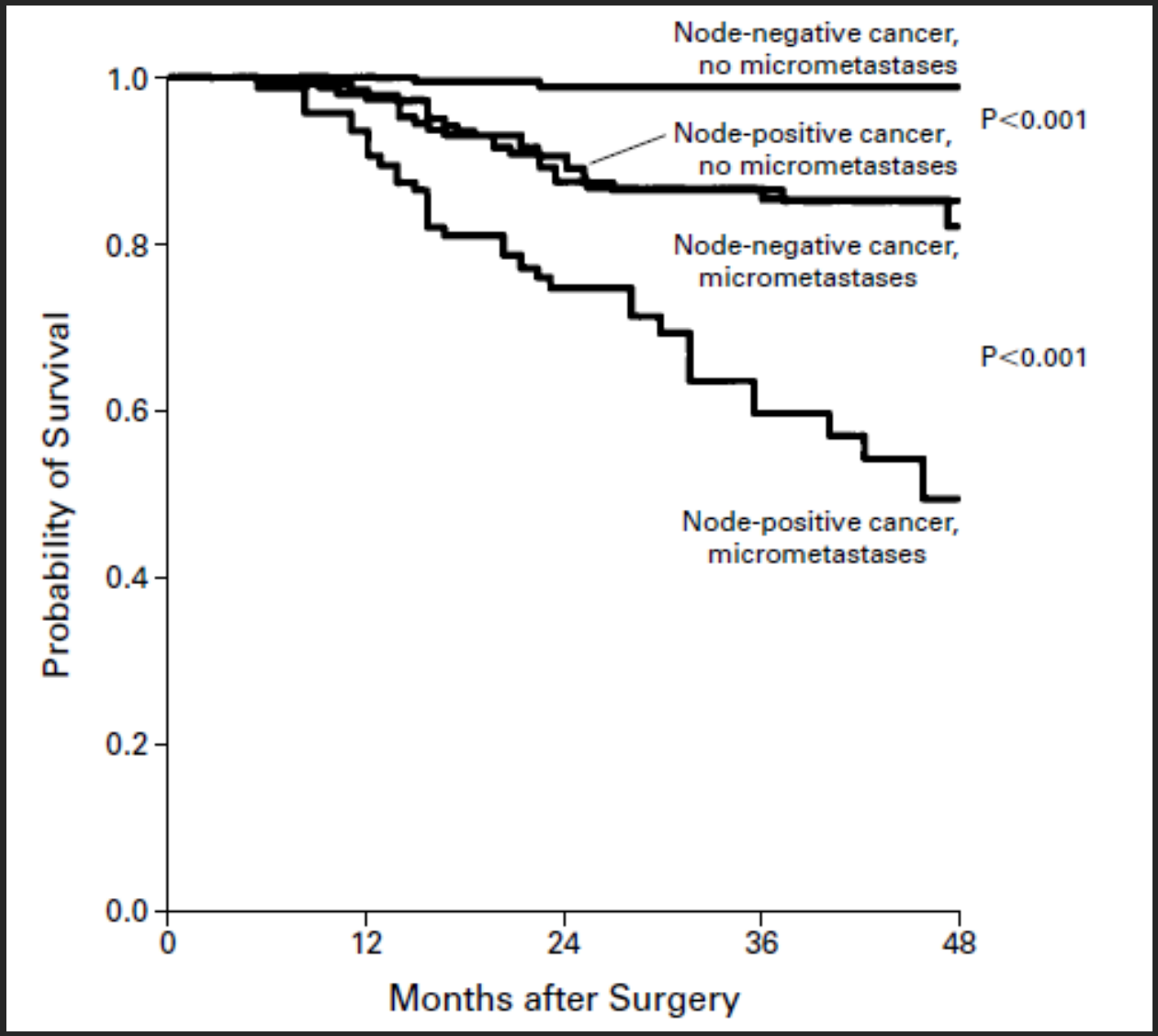
Lessons from CML

- Molecular testing of Bcr-Abl is an effective clinical tool
  - Associated with CCyR, progression, survival, and complete molecular remission
  - Peripheral blood testing is easy, relatively cheap
- A lot of this was luck
  - Different control genes worked
  - MMR turned out to be a robust surrogate even though not strongly linked to biology
- Nonetheless, molecular monitoring got into ELN and NCCN guidelines and into phase 3 trials as endpoints *without*
  - Widespread standardization
  - Regulatory approval

Case study: circulating tumor cells

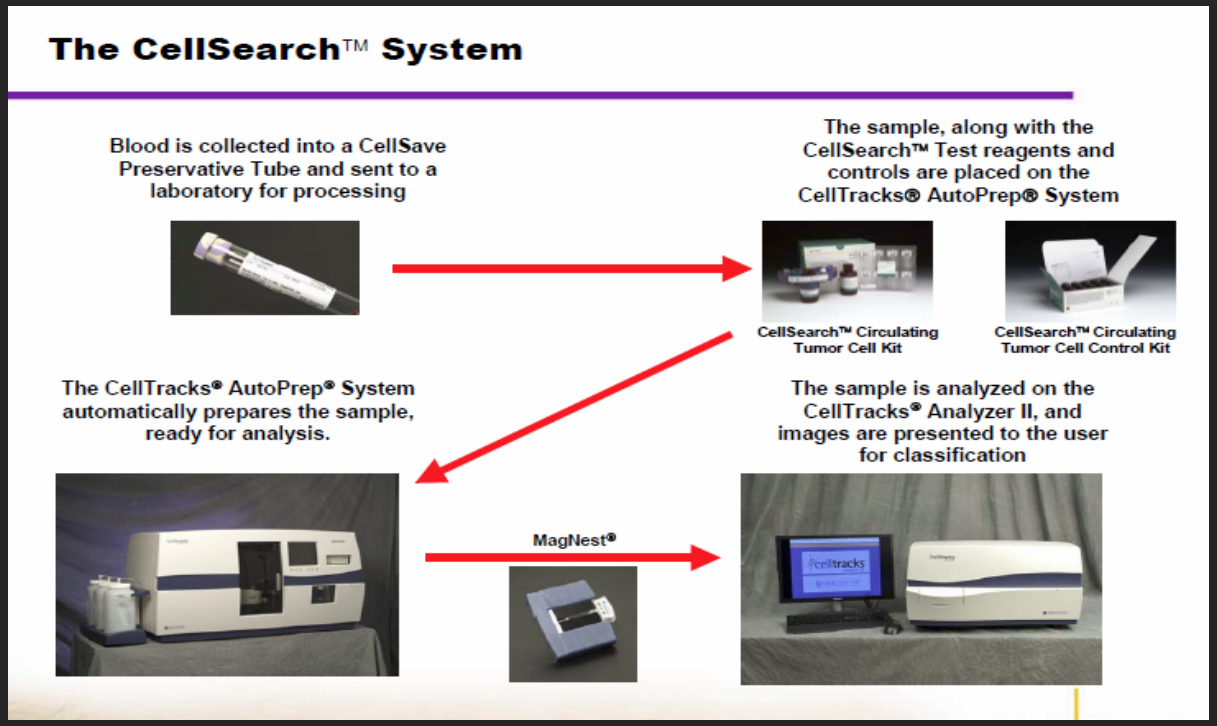
- What are CTCs?
  - Cells originating in a primary solid tumor that are detected in the bloodstream…
  - Dying cells?
  - Precursors of metastasis??
  - Cancer stem cells??
  - Self-seeding for primary tumor??

Braun et al., 2000 (CK staining, BM)



Advances-CellSearch® device:

- CellSave tube with 7.5 ml blood →
- Capture with EpCAM-ferrofluid →
- Semi-automated flow cytometric analysis
- CTC defined as:
  - Nucleated cell (DAPI positive)
  - Cytokeratin 19-positive
  - CD45-negative



Analytic validity: Allard et al., 2004

- Multi-center study:
  - Accuracy, sensitivity and linearity of detection in spiked samples
  - Reproducibility across duplicate tubes and multiple operators
  - Prevalence of CTCs in patients with early or late stage solid tumors

Clinical Validity: Cristofanilli et al., 2004

- Multicenter prospective study of 177 patients with metastatic BrCa, CTCs measured at beginning of new systemic treatment and 3-4 weeks later.

- A CTC count of 5 or more per 7.5 ml of blood at any time during the course of the disease is predictive of shorter progression-free survival and overall survival.

FDA Clearance-detection

For *in vitro* diagnostic use.

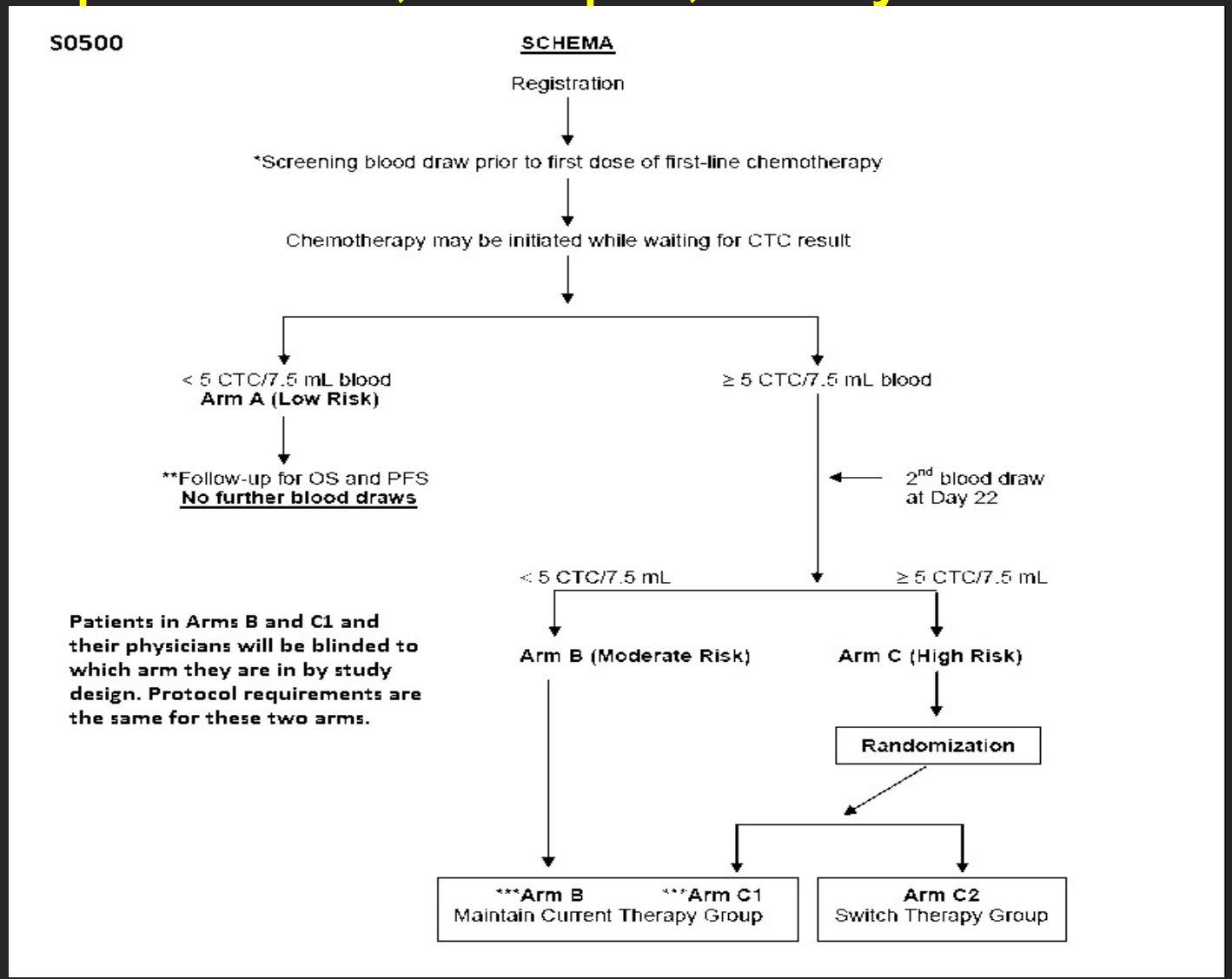
The CellSearch™ Circulating Tumor Cell Kit is intended for the enumeration of circulating tumor cells (CTC) of epithelial origin (CD45-, EpCAM+, and cytokeratins 8, 18+, and/or 19+) in whole blood.

The presence of CTC in the peripheral blood, as detected by the CellSearch™ Circulating Tumor Cell Kit, is associated with decreased progression free survival and decreased overall survival in patients treated for metastatic breast, colorectal or prostate* cancer. The test is to be used as an aid in the monitoring of patients with metastatic breast, colorectal or prostate cancer. Serial testing for CTC should be used in conjunction with other clinical methods for monitoring metastatic breast, colorectal and prostate cancer. Evaluation of CTC at any time during the course of disease allows assessment of patient prognosis and is predictive of progression free survival and overall survival.

End of story-what do you do?

- CLINICAL UTILITY: whether the results of the test provide information that can contribute to and improve current optimal management of the patient's disease

S0500-advanced disease, first line rx open 2006, 624 pts, analysis 2015



Lessons Learned

- FDA clearance process provided evidence on analytic and clinical validity, but limited evidence on clinical validity
- Design of multi-center trial required demonstration of inter-laboratory reproducibility—not covered by CLIA
- Entire process from prototype device to clinical trial took >10 years and significant investment from both sponsor and NCI
  - *How many times can we afford to do this again?*
  - *How do we integrate new technology???*

C-11 Choline as a Response Marker-FDA approval

- FDA approved 2012 (old agent)
- approval limited to a single manufacturing site — the Mayo Clinic in Rochester, Minnesota
- Indication: "…to detect recurrent prostate cancer…in men with a rising PSA after prior treatment for prostate cancer…to detect tumors that are not detectable by conventional scanning methods (e.g., bone scans and CT scans). "

Conclusions

- FDA approval of C-11 choline was based on historic clinical use and is not a generalizable model for establishing clinical utility of future imaging assays.
- Establishing the technical validity of imaging assays has some issues significantly different from IVD's, but establishing the clinical utility should conceptually be the same.

Summary: What are you measuring, and what is the endpoint?

- Measurement:
  - Used as measurement of response
  - Used as measurement of relapse
  - May (or may not) be associated with therapy
- Endpoint (best endpoint depends on disease)
  - Survival
  - Relapse
  - PFS, TTP (time dependent)
- Evidence: retrospective -> prospecti
- ALSO: Defeat the urge to make the continuous, quantitative variable categorical

How do we get there?

What can the NCI do?

- Newly mint platinum coins, distribute to participants of this meeting
- Biomarker network-facilitate more inter-site standardization and reproducibility of assays BISQFPT *redux*
- Explore potential to support of IDE application
- Incentivize more companion biomarker studies in cooperative group therapy trials
- Facilitate biomarker research for orphan diseases, under-served populations.
- Assist CMS in developing its coverage with evidence development (CED) reimbursement pathway.

What can academia do?

- Pay more attention to assay design and operating characteristics
- Design innovative clinical trials using markers to drive therapy or as surrogate outcomes
- Collaborate with other academia, NCI, industry and professional organizations to “standardize” assays

What can industry do?

- Support monitoring studies (e.g., CML)
- Create standards (with NCI and professional organizations?)
- Work with NCI, academia on patent issues
- Support companion dx and IDE development

What can FDA do?

- Weigh IDE v. risk and incidence/prevalence
- Consider paths to replace prevailing tests with newer technology
- Meet with NCI, academia, industry to plan the future explosion of technology and tests