

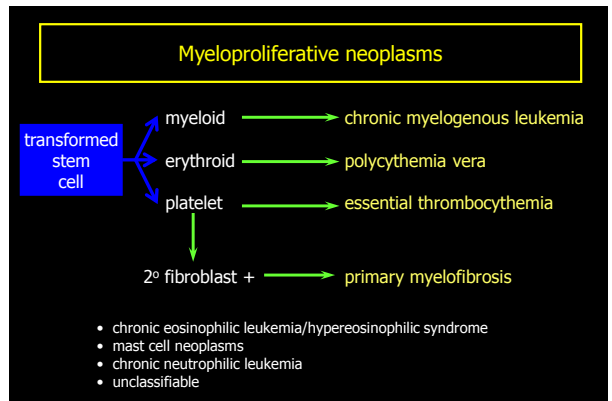


## Diagnostic Molecular Pathology of Myeloid Neoplasms

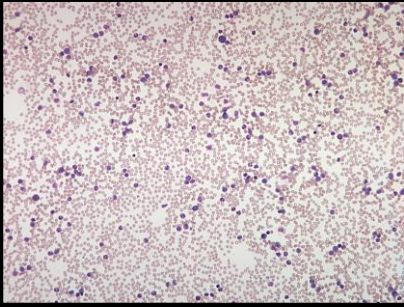
23<sup>rd</sup> Congress of The Arab Division  
International Academy of Pathology  
Beirut, Lebanon  
Tuesday November 29, 2011: Pre-congress workshop

Adam Bagg  
University of Pennsylvania  
Philadelphia, USA

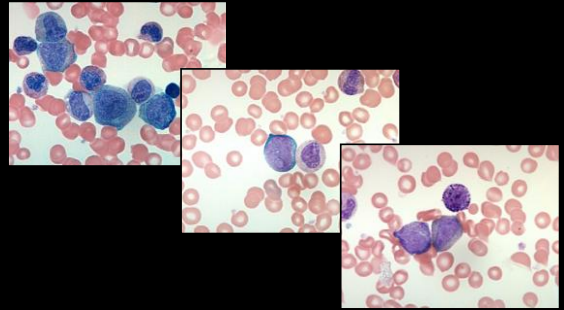
## Myeloid neoplasms



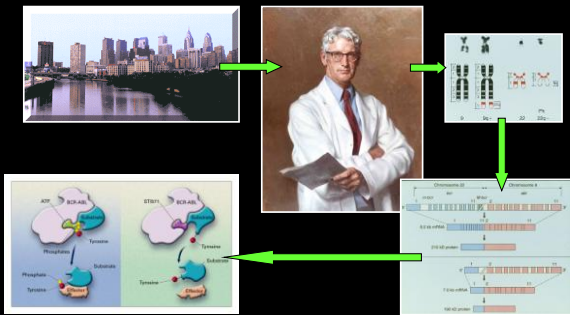
### Chronic myelogenous leukemia



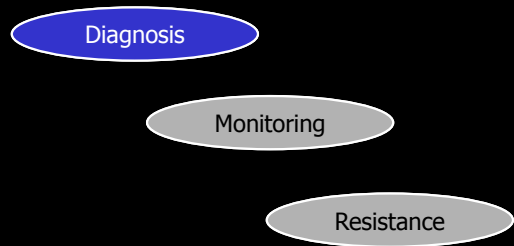
### Chronic myelogenous leukemia

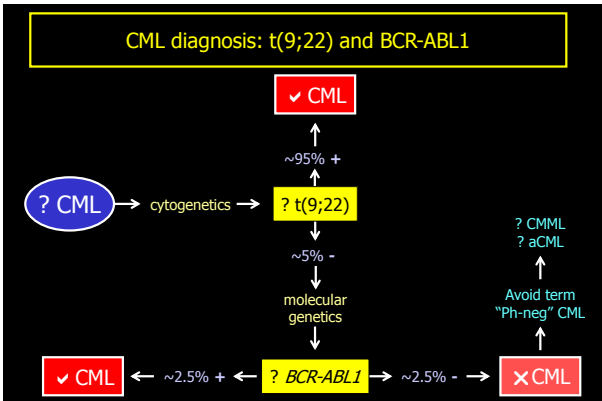
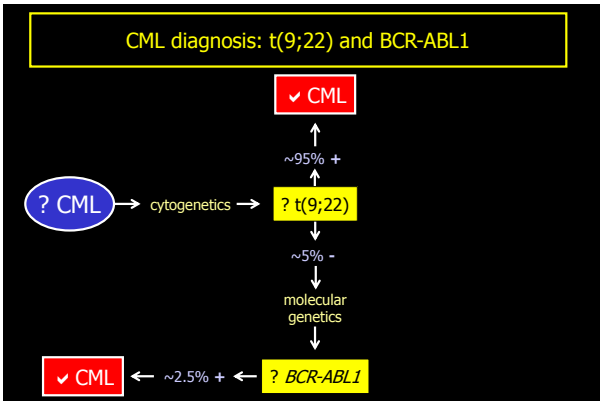
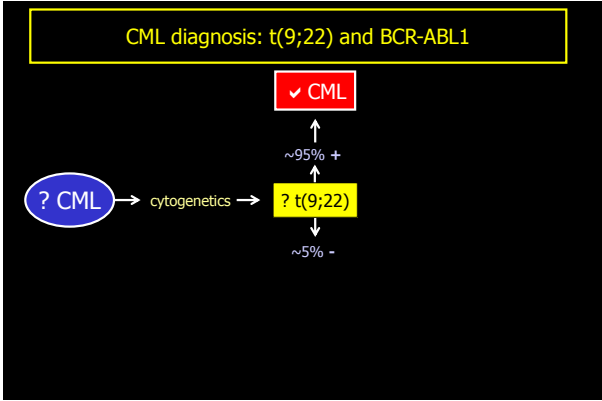
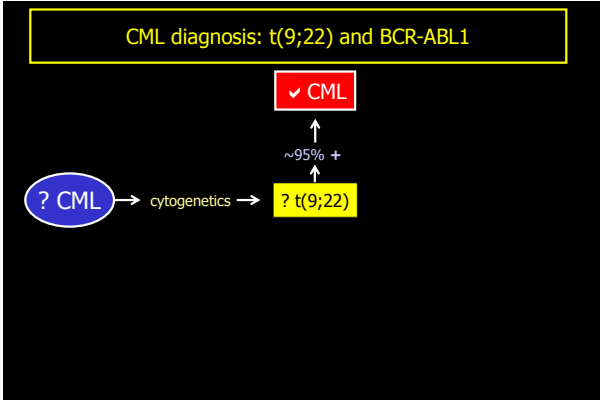


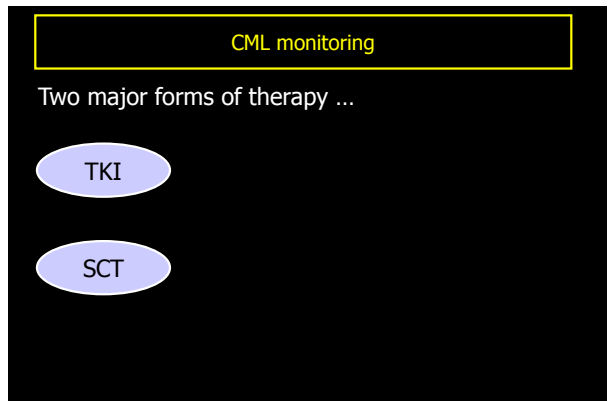
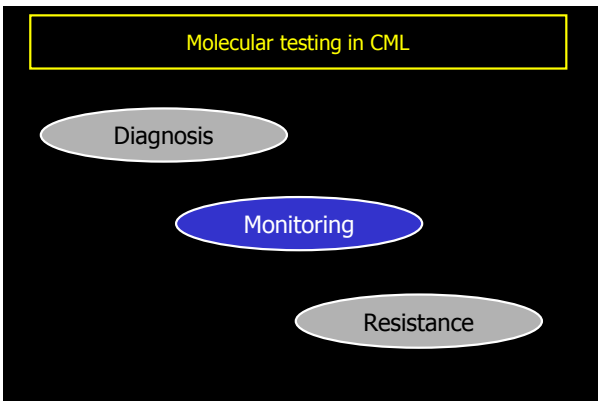
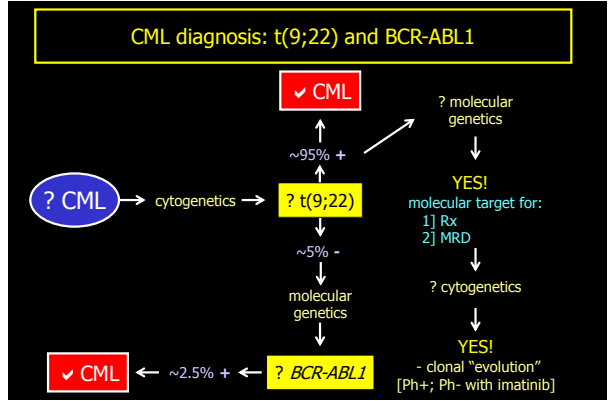
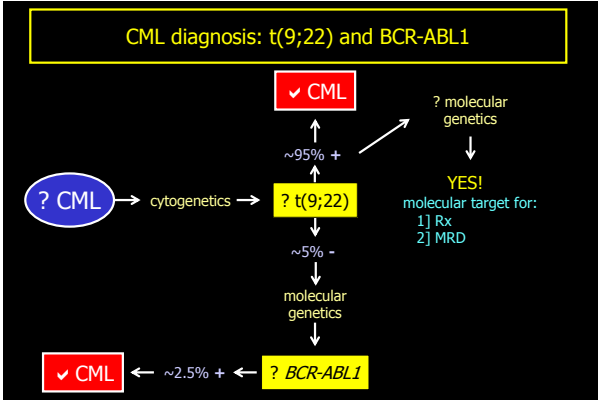
### The Philadelphia story

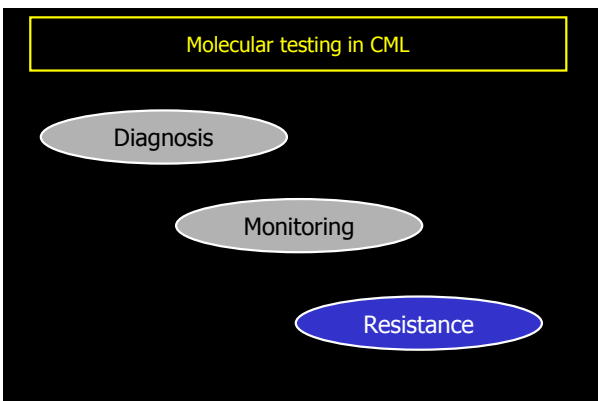
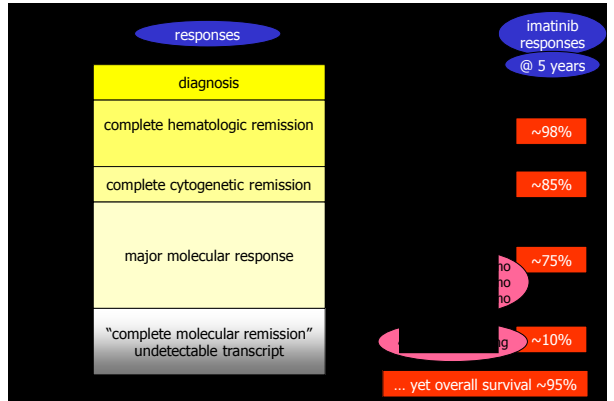
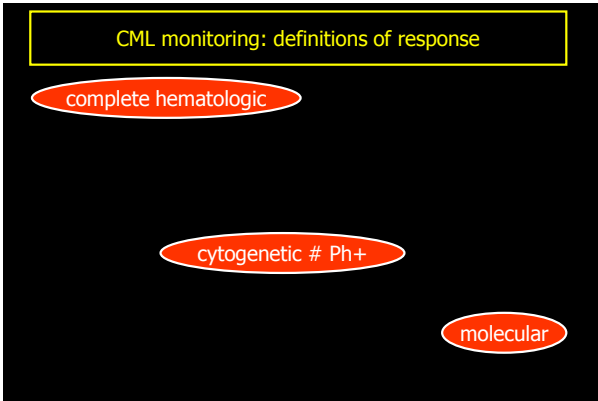


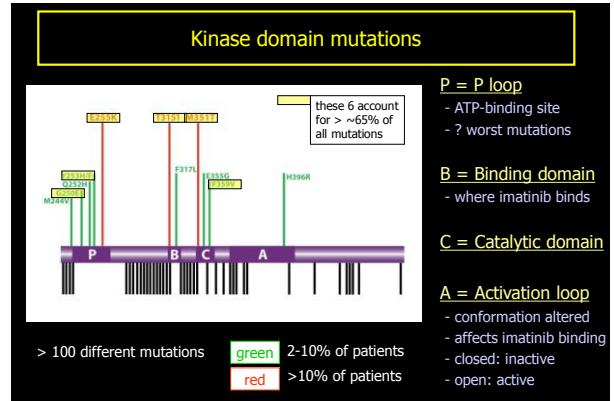
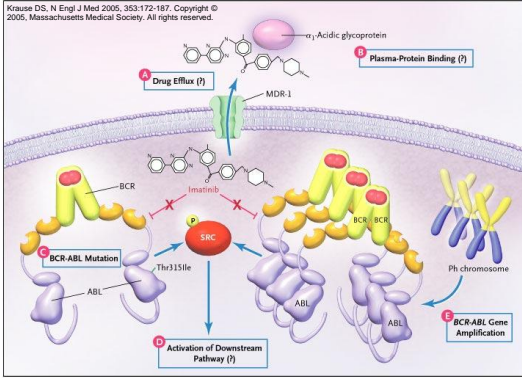
### Molecular testing in CML











### Kinase domain mutations

- most common cause of resistance
- not induced by Rx
- ? BCR-ABL1 induced
- not all are created equally

### Indication for mutation testing

- treatment failure/  
suboptimal response
- loss of response
- anyone in AP or BC

### Genetic testing in CML: summary

Diagnosis

Monitoring

Resistance



### Molecular and other testing in non-CML MPNs

pre-2005 ...

	karyotype	genes	PRV1	EEC	↓ mpl megs	↓GATA1 megs	↑ circ CD34+
PV	9p+, +8+9	?	+	+	+	?	-
ET	?	?	+ [50%]	+ [50%]	+/-	?	-
PMF	del(13q14)	?	-	-	+/-	+	+
PPMF	1q+	?	?	?	?	?	?

### Molecular and other testing in non-CML MPNs

post-2005 ...

	karyotype	genes	PRV1	EEC	↓ mpl megs	↓GATA1 megs	↑ circ CD34+
PV							
ET							
PMF							
PPMF							

JAK2 V617F mutation (etc)

## JAK2 is out of the box ...

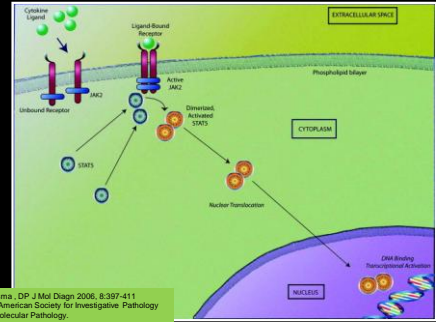


- **Just Another Kinase**
  - one of many cloned at the time (1989)
- **Janus Kinase**
  - two-headed Roman god of gates and passages

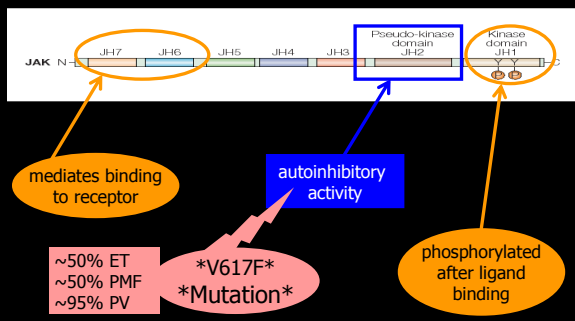
- non-receptor tyrosine kinase (TK)
- has 2 TK domains (**hence the name**)
  - most TKs have only 1
- 4 members of JAK family
  - JAK1, JAK2, JAK3 and TYK2



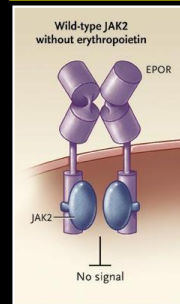
## JAK-STAT pathway



## JAK2 structure, function, mutation

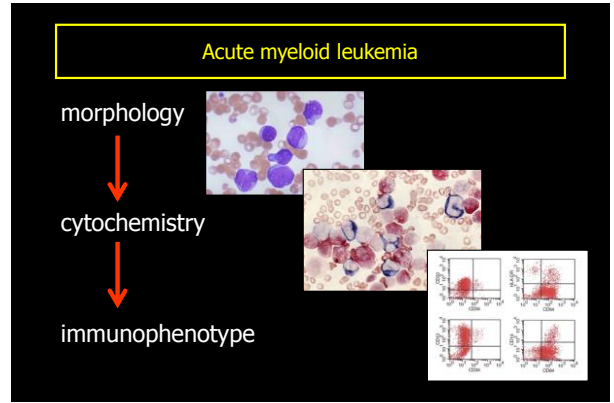


## JAK2: wild-type and mutant



Campbell P. N Engl J Med 2006, 355:2452-2466. Copyright © 2006, Massachusetts Medical Society. All rights reserved.





Acute leukemia

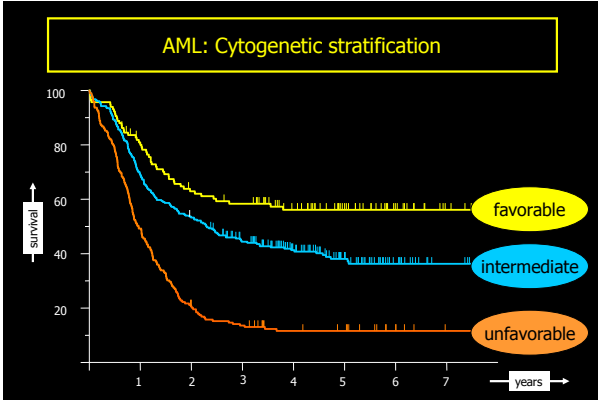
(cyto)genetics

the most important  
diagnostic test in  
acute leukemia

AML: Cytogenetic stratification

Risk group	Genetics	Frequency	CR	5yr Survival
Favorable	t(8;21) t(15;17) inv(16)	~25%	~85%	~60%
Intermediate	normal +8, +21 11q23*	~50%	~80%	~40%
Unfavorable	-5, -7 3q complex	~25%	~60%	~15%

\* t(9;11) only – others = unfavorable  
Combined data from CALGB, UK-MRC and US-intergroup for "young" AML



### AML: Cytogenetics

**The big 4** → *sine qua non* for WHO<sup>©</sup>

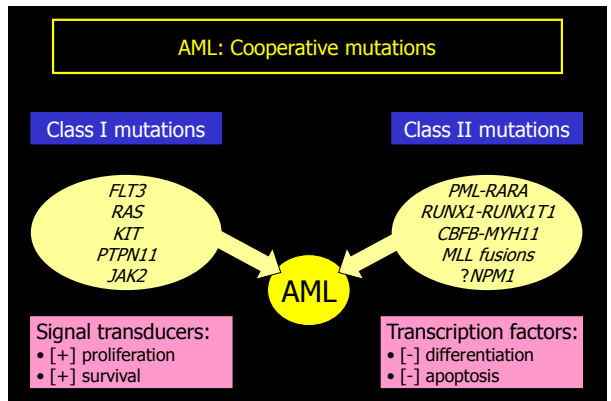
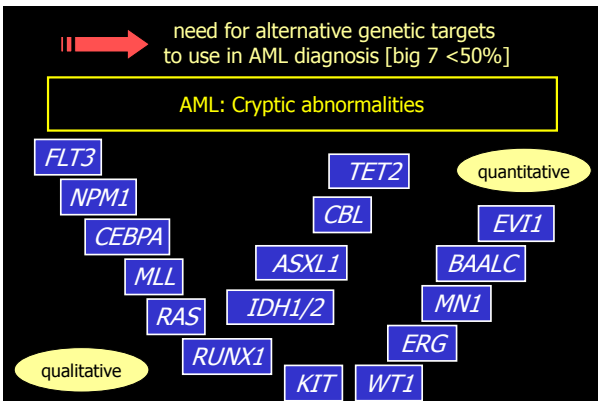
- t(15;17) [M3] ~10%
- t(8;21) [M2] ~10%
- inv(16) [M4Eo] ~10%

GOOD

- t(11q23)\* [M4/M5] ~5 - 10%

not so good

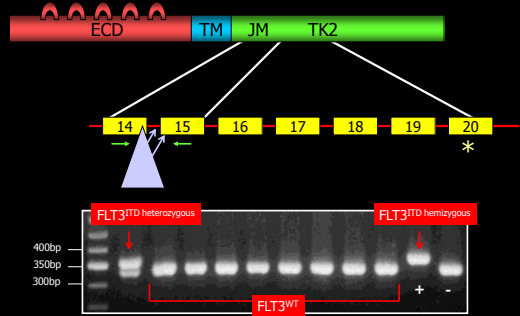
© 2001 → 2008 = big 7 [added t(1;22), t(6;9) and inv(3)—all bad; t(9;11) specifically]  
\* promiscuous (>30 partners); FAB for translocations only - PTD [M1/M2]



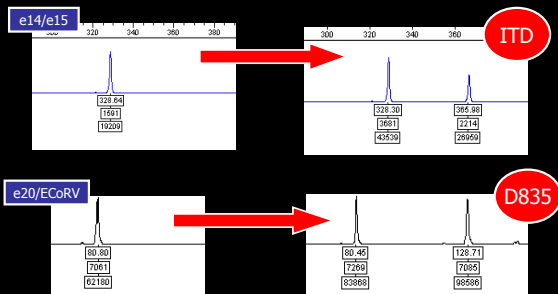
## FLT3

- 2 types of genetic abnormalities described:
  - ITD of JM region ~23% PCR
  - Asp835 missense mutation ~7% RE-PCR
  - ~30%

## FLT3 : genotyping



## FLT3 : multiplex PCR on CE



## FLT3

- One of the most common known molecular targets in AML

## NPM1

## AML: Cytogenetics vs Molecular

## AML: FISH vs Molecular

- each has advantages and disadvantages
  - diagnostic sensitivity:
  - analytic sensitivity:
  - numeric abnormalities:

## AML: Genetics – WHO 2008

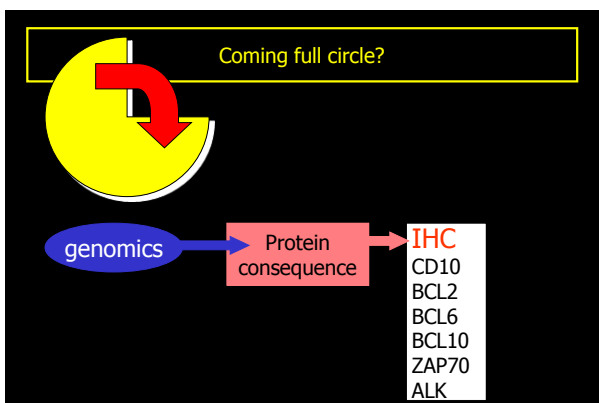
Karyotype	Genes	Morphology	Frequency	Prognosis
t(8;21)	RUNX1/RUNX1T1	M2	~5%	good
t(15;17)	PML/RARA	M3	~5-8%	good
inv(16)	CBFB/MYH11	M4Eo	~5-8%	good
t(9;11)	MLL3/MLL	M4/M5	~2%	intermediate
t(1;22)	RBM15/MKL1	M7	<1%	poor
t(6;9)	DEK/NUP214	Basophila	~1%	poor
inv(3)	RPN1/EVI1	MLD	~1%	poor
	NPM1 mutations*	M4/M5	~30%	good
	CEBPA mutations*	M1/M2	~10%	good

\* AMLs with mutated *NPM1* and *CEBPA* = provisional entities  
 AMLs with *FLT3* not an "entity" but testing "strongly recommended"



Immediate potential Rx applications ...

Disease	Genotype	Rx relevance
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The last slide ...

- Powerful ... but one piece of the puzzle

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- Positive result: not always = neoplastic

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### The last slide ...

- Powerful ... but one piece of the puzzle
- Positive result: not always = neoplastic
- Negative result: not always = not neoplastic
- Integrate: with morphologic, immunophenotypic, clinical data
- Decision to perform/ability to interpret: contextual
- More rational, biologically-based diagnosis:  
    → more appropriate, targeted Rx

### Any questions ...

