Requirements of Physicians for Standardized/Comparable Measurements: Impact on Medical Decisions

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Medical Decisions

- Diagnostic
  - Separation of patients into categories.
  - Evaluation of a patient's single test value relative to distribution of values from patients having confirmed diagnoses (Reference data generally collected at a different time and often with a different assay).

Medical Decisions (continued)

- Monitoring
  - Tracking of a patient's multiple test values over time (maybe hours, day, weeks, months or years)
  - Evaluation of test value relative to prior values and/or relative to therapeutic range (generally established with a different assay or different assay calibration)

Laboratory Performance Criteria

- Diagnostic Test
  - Major dependence on analytic bias for effects on health system performance. Dependence on both bias and precision for individual patient performance.
- Monitoring Test
  - Major dependence on both analytic bias and analytic precision for both health system performance and individual patient performance.

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Two Analytic Control Issues

- Precision (scatter)
- Accuracy (bias)

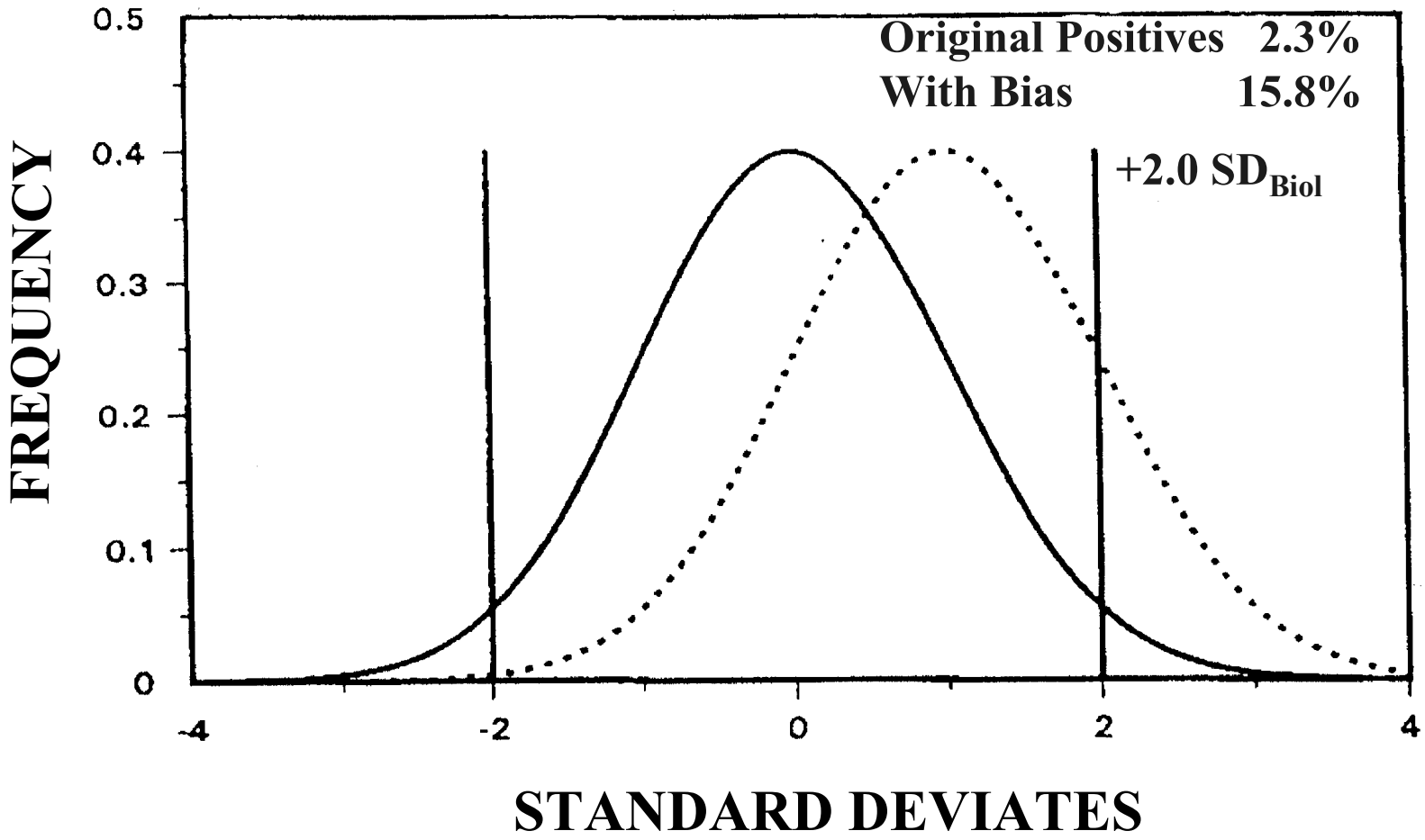
Criteria for "Acceptable" test results

- Depends on clinical application
- Medical guidelines with fixed decision limits accentuate problems with analytic bias
- Biologic variability can be used to bound the precision requirements
- Therapeutic Drug Intervals can be used to bound the precision of drug assays

Tolerance Limits for Analytic Bias

- Bias directly affects test values
- Small analytic changes can produce major shifts in frequency distributions of clinical test values

Effect of Analytic Bias on Decisions



Laboratory Tests as Key Indicators for Clinical Guidelines

- Cholesterol - Cardiac Disease Risk
- PSA - Prostate Cancer Detection

Paradigm I: Cholesterol testing for identifying patients at risk for coronary artery disease (CAD)

National Cholesterol Education Program (NCEP)

- Test adults > 20 years, every 5 years

- Follow-up if cholesterol ≥200mg/dL or HDL Cholesterol < 40mg/dL

- LDL cholesterol goal for persons with CAD is 100 mg/dL

- LDL cholesterol goal for persons with 2+ risk factors is < 130 mg/dL and < 160 mg/dL for these with 0-1 risk factors

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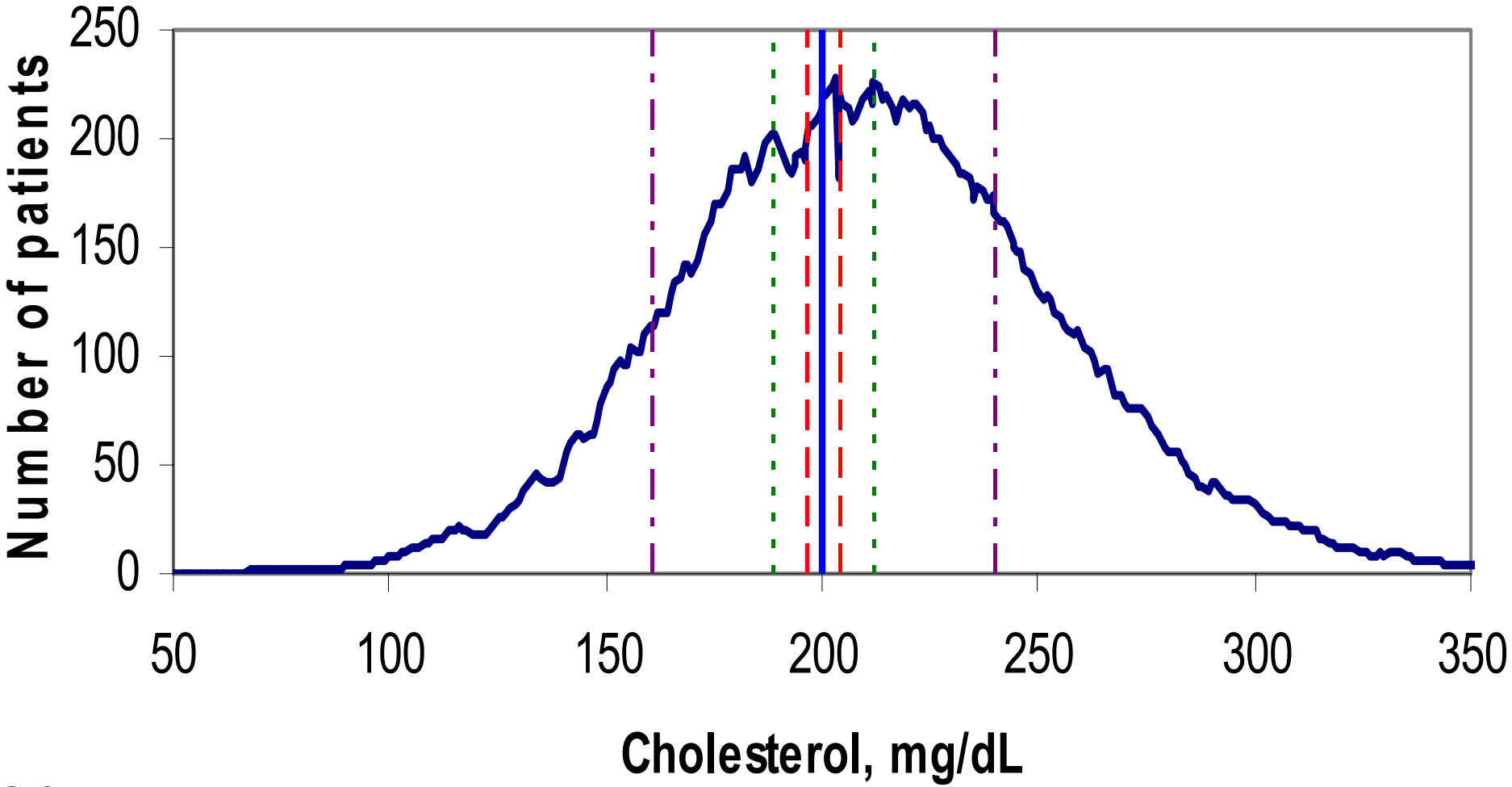
Cholesterol Frequency Distribution with ±2%, ±6% and ±20% Limits Around 200mg/dL



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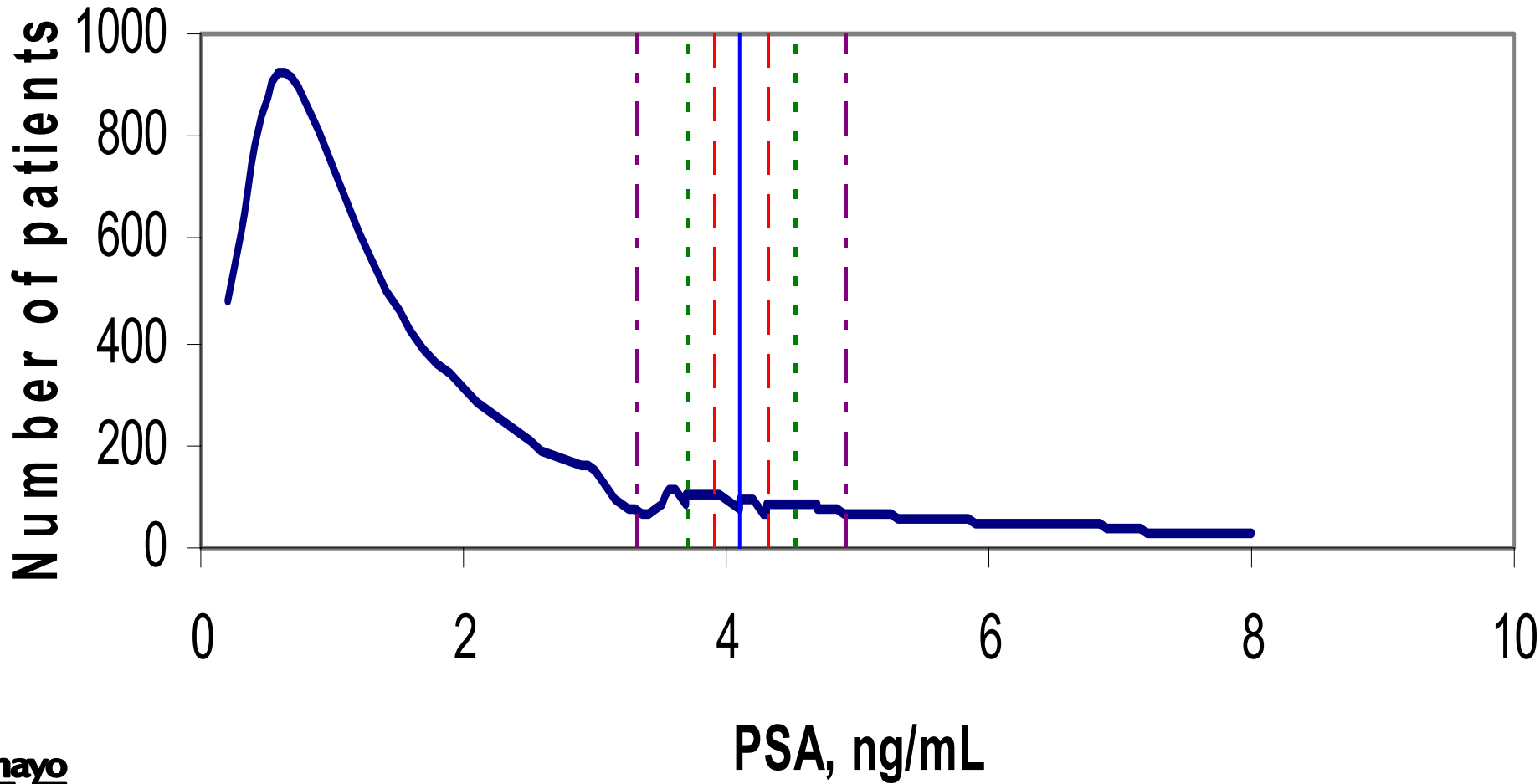
Cholesterol Bias Effects on Positives per 1000 @ 200 mg/dL

Bias	Number	Percentage
-10% bias	410	-31.0%
-3% bias	538	-9.4%
-1% bias	575	-3.2%
0% bias	**594**	**0%**
+1% bias	612	+3.0%
+3% bias	646	+8.8%
+10% bias	759	+27.8%

Paradigm II: Prostate-specific antigen (PSA) in prostate cancer screening

- American Cancer Society and American Urology Association recommend offering annual screening with PSA and DRE for men >50y (or >40y for high risk groups)
- Follow-up set at 4.0 ng/mL or age specific reference limits
- Prostate biopsy is recommended follow-up

PSA Frequency Distribution with ±6%, ±10% and ±20% Limits around 4ng/mL



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PSA Bias Effects on Positives Per 1000

Level	4.0 ng/mL		6.0 ng/mL	
-20% bias	144,	-18.2%	87,	- 21.6%
-10% bias	160,	-9.1%	98,	-11.7%
-6% bias	165,	-6.3%	103,	-7.2%
0% bias	**176,**	**0%**	**111,**	**0%**
+6% bias	184,	+4.5%	119,	+7.0%
+10% bias	196,	+11.4%	126,	+13.5%
+20% bias	220,	+25.0%	144,	+29.7%

Tolerance Limits for Precision

- Analytic precision is clinically filtered by biologic variation
- If analytic SD <1/4 biologic SD, total SD only increases by 3%

Impact of Analytic SD on Total SD

- $SD_{TOTAL} = \sqrt{SD^2_{ANALYTIC} + SD^2_{BIOLOGIC}}$
- If $SD_{ANALYTIC} < 0.25\ SD_{BIOLOGIC}$
- $SD_{TOTAL} \leq \sqrt{(0.25)^2\ SD^2_{BIO} + (1.0)^2\ SD^2_{BIO}}$
- $SD_{TOTAL} \leq 1.03\ SD_{BIOLOGIC}$

Targets for Therapeutic Drug Monitoring Based on Therapeutic Interval (C_{upper} - C_{lower})

- Glick: CV $\leq$ 0.1 (C_{upper} - C_{lower}) /C_{upper}
- Burnett: CV $\leq$ (C_{lower}/6) /C_{upper}
- Fraser: CV $\leq$ 0.25 [($2^{T/t}$ -1)/($2^{T/t}$ +1)]

Ref: Arch Pathol Lab Med - 125:729-735, 2001

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Allowable Imprecision for TDM/CV's (as percentages)

Drug	Glick	Burnett	Fraser
Digoxin	6.0	6.7	2.2
Lithium	5.0	8.3	2.2
Phenobarbotal	7.5	4.2	0.6
Phenytoin	5.0	8.3	2.3
Procainamide	6.0	6.7	7.5
Theophylline	6.7	5.6	4.0

College of American Pathologist % Labs NOT meeting criteria in 1999

Test	Glick	Burnett	Fraser
Digoxin	30.0	25.0	100
Lithium	21.4	0.0	100
Phenobarbotal	9.1	54.0	100
Phenytoin	25.0	8.3	100
Procainamide	0.0	0.0	0
Theophylline	15.4	38.5	62
Total Not Meeting Criteria	**21.9**	**25.4**	**77**

Mayo Health System
Integration of Physician Practice and Patient Referrals

Five States (MN, IA, WI, AZ, FL)

62 Medical Facilities

19 Hospitals, 4037 beds

4600 Physicians/Trainees

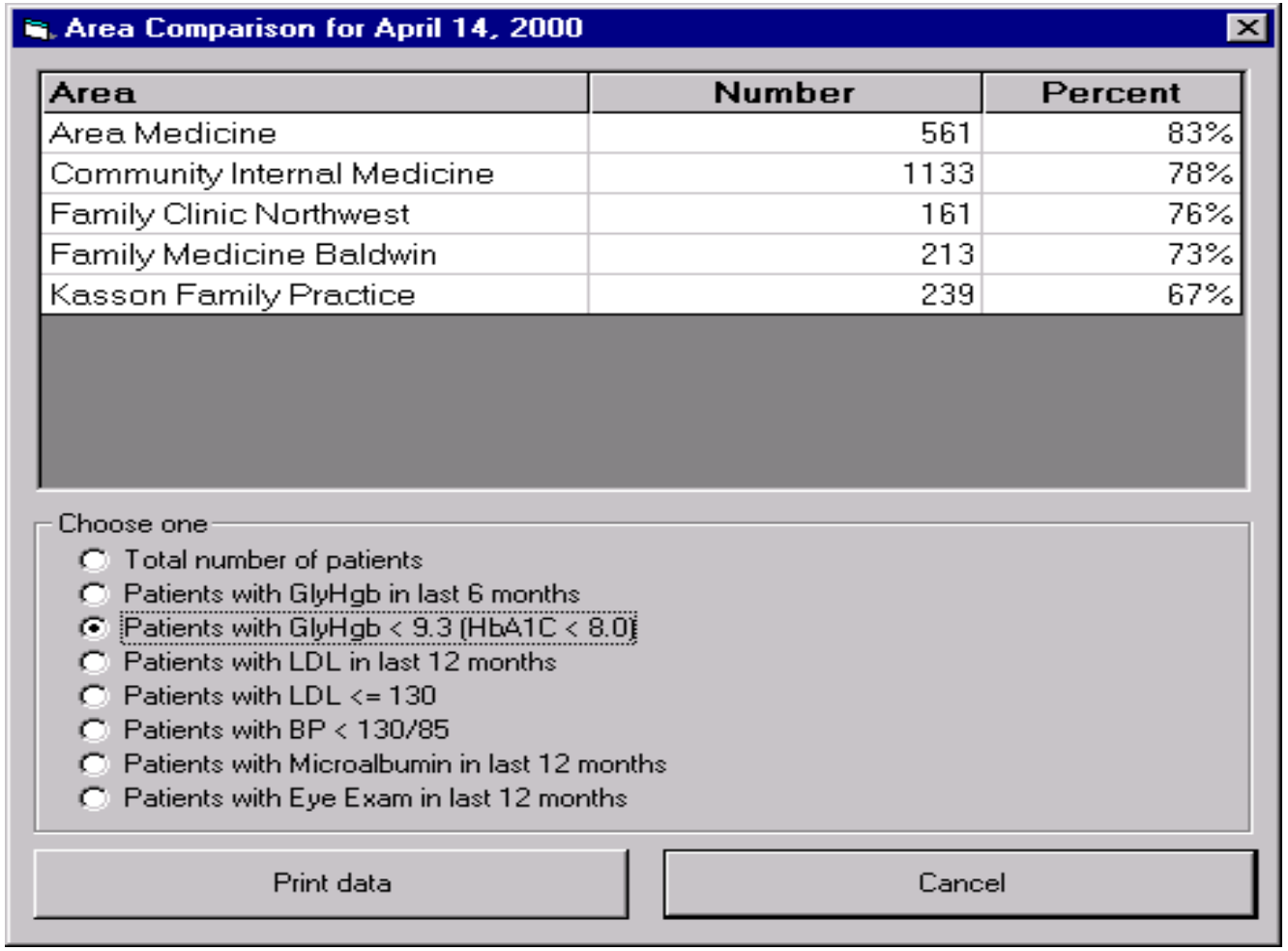
17,600,000 Laboratory Tests per year

Mayo Foundation

Mayo/ICSI Guidelines

- 67 Primary Care Guidelines developed (Generally implemented through-out Mayo Health System)
- Evidence Based, Often have fixed numeric decision limits for laboratory tests
- Annual Review of performance and updates

Laboratory Performance Can Directly Affect "Clinical Outcomes Monitoring"



Summary

- Analytic Bias can profoundly affect patient classifications (diagnoses) with guidelines
- Biologic variation and therapeutic intervals can help define precision requirements for monitoring tests
- Combined medical, government, and industry cooperation is needed to define analytic tolerance criteria and performance of commercial instruments and reagents

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