Then ….

Now ….

Next ….

2009 Executive War College

April 28, 2009

Presented by: Marc D. Grodman, MD, CEO

2009

New Strategies

for Clinical Laboratories:

Leveraging the Assets

Marc D. Grodman, M.D.
CEO, Bio-Reference Laboratories, Inc

Presented at War College 2000

CEO Summit Day

May 18, 2000

2000

The Evolved Clinical Laboratory

Presented at:

2001 Executive War College

Cincinnati, Ohio

May 8, 2001

by: Marc D. Grodman, MD, CEO

Bio-Reference Laboratories, Inc. - NASDAQ: BRLI

2001

The Lab Demise

- Reimbursement rate
- Poor performance of market leaders
- Hint of scandal
- Advent of Managed Care

2000

The No-Lab Lab

"**Just because you do laboratory testing,**

you don't have to call yourself a Laboratory."

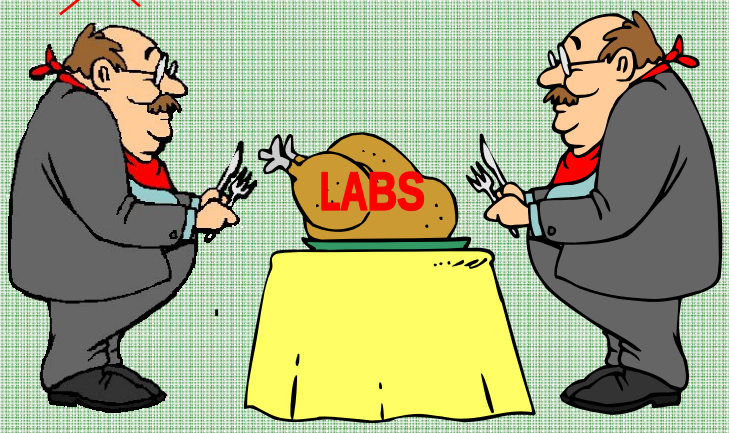
Public Relations Consultant, 1998

2000

"Wherever Managed Care is leading Healthcare, clinical laboratories must insist on a place at the table"

Ex-CEO

The ~~C~~EO of a Major National Laboratory, 1993



2000

The Worst Performers

10-Year

	COMPANY NAME	STOCK SYMBOL	RETURN
1	Novell	NOVL	-17.1%
2	Kmart	KM	-12.1
3	Dillard's	DDS	- 8.5
4	Sicor	SCRI	- 7.6
5	IMC Global	IGL	- 6.4
6	Rite Aid	RAD	- 5.5
7	Lab. Corp. of America Holdings	LH	- 5.3
8	Readers' Digest Association	RDA	- 4.8
9	Conseco	CNC	- 4.8
10	Service Corp. International	SRV	- 4.6

The Best Performers

3-Year

	COMPANY NAME	STOCK SYMBOL	RETURN
1	OSI Pharmaceuticals	OSIP	+143.0%
2	Medarex	MEDX	+128.0
3	Laboratory Corp. of America Holdings	LH	+127.4
4	CV Therapeutics	CVTX	+122.1
5	ImClone Systems	IMCL	+117.3
6	Idec Pharmaceuticals	IDPH	+106.5
7	Cephalon	CEPH	+103.3
8	Abgenix	ABGX	+102.3
9	Quest Diagnostics	DGX	+100.4
10	Ensley	ENSY	

FACTORS WHICH HAVE CONTRIBUTED TO INCREASING VALUE IN THE CLINICAL LABORATORY INDUSTRY:

- ❖ Increase in Esoteric Testing
- ❖ Consolidation of the Lab Industry
- ❖ Improvement in Reimbursement Rates
- ❖ Expanded Role of Lab Testing
- ❖ Aging of the Population

Labs w[illegible] inal

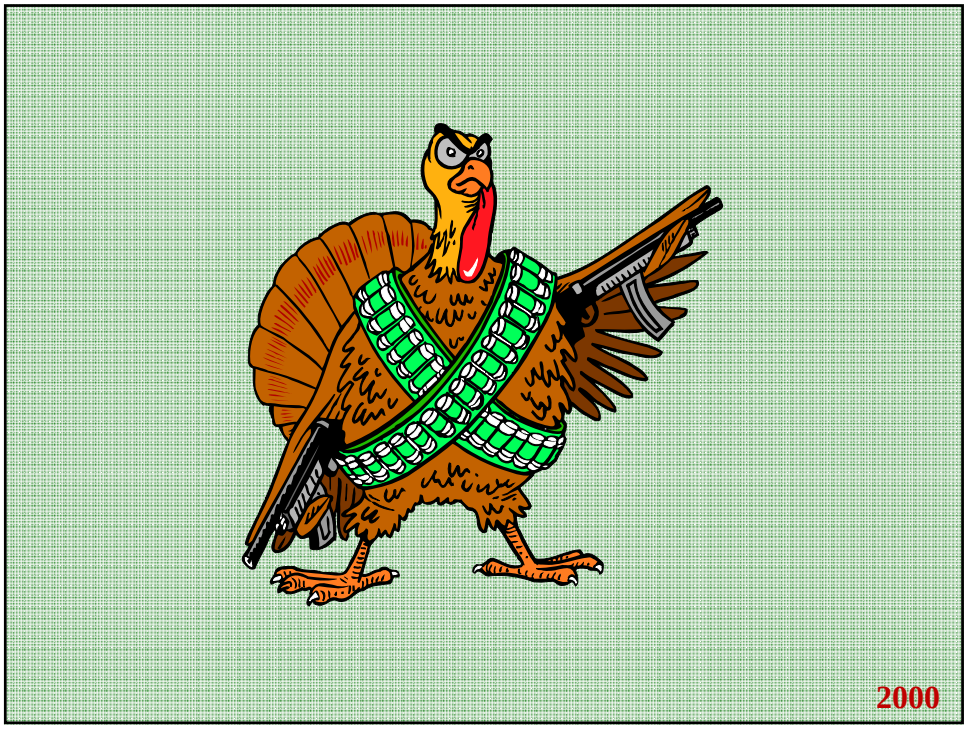
[illegible] present more

[illegible] related to lab test

opportunities for regional, community labs

And probably not as great as thought now

2001



2000

2009

Clinical Laboratories are even better

than what they seemed at that time

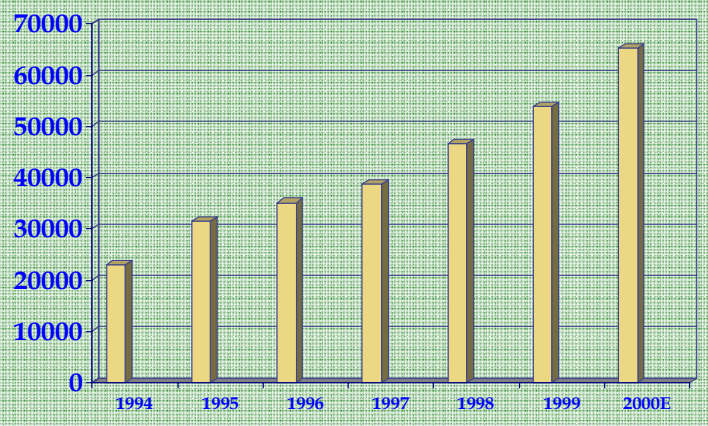
Bio-Reference Laboratories, Inc.

- Over 800 full and part time employees
- Over 2,000 full and part time employees
- Direct sales force of approximately 30 people
- Direct sales force of approximately 150 people
- Processed and reported over 2 million lab reports in FY 00
- Processed and reported over 4 million lab reports in FY 08

2001 2009

Bio-Reference Laboratories, Inc.

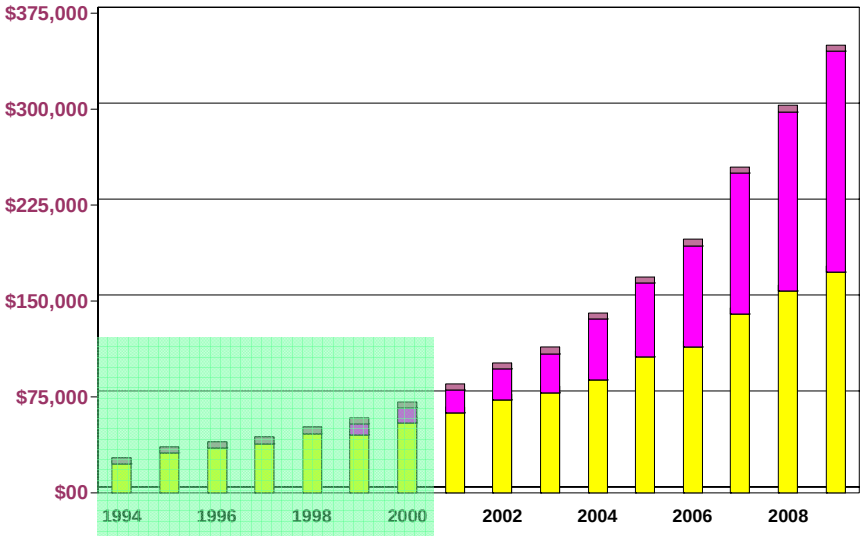
REVENUE, IN MILLIONS



2000

BRLI: Esoteric Testing has Fueled Growth

BRLI has demonstrated 20% CAGR over the past fifteen years.

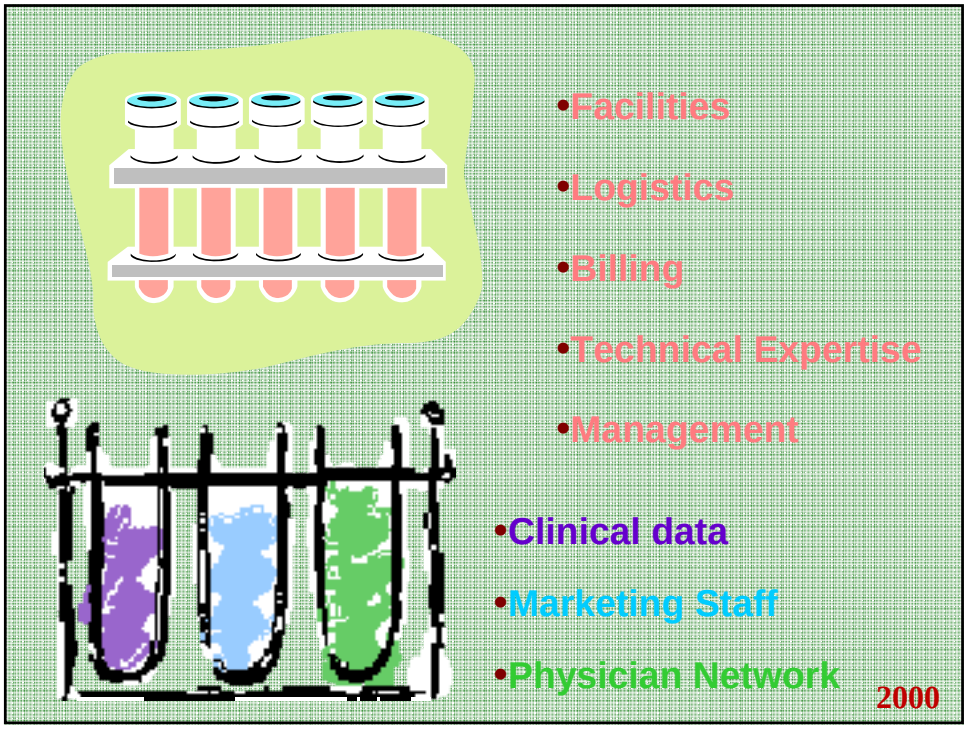


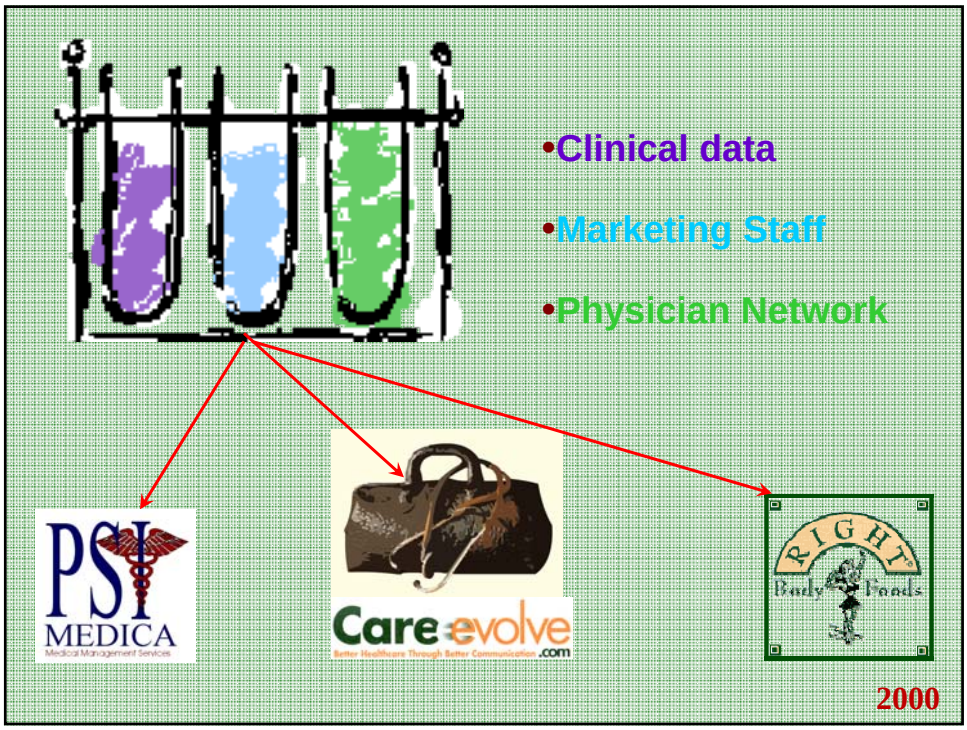
2009

Axioms for Growth

- The clinical laboratory will only realize its full value by leveraging its underlying assets.
- Laboratories are defined by the markets they serve.
- Clinical Laboratories have a translational role to educate and facilitate physicians' use of new science and technology in order to answer questions of clinical relevance

2009


•Facilities
•Logistics
•Billing
•Technical Expertise
•Management
•Clinical data
•Marketing Staff
•Physician Network
2000


•Clinical data
•Marketing Staff
•Physician Network
PSI MEDICA
Medical Management Services
Care evolve
Better Healthcare Through Better Communication .com
RIGHT
Body Foods
2000

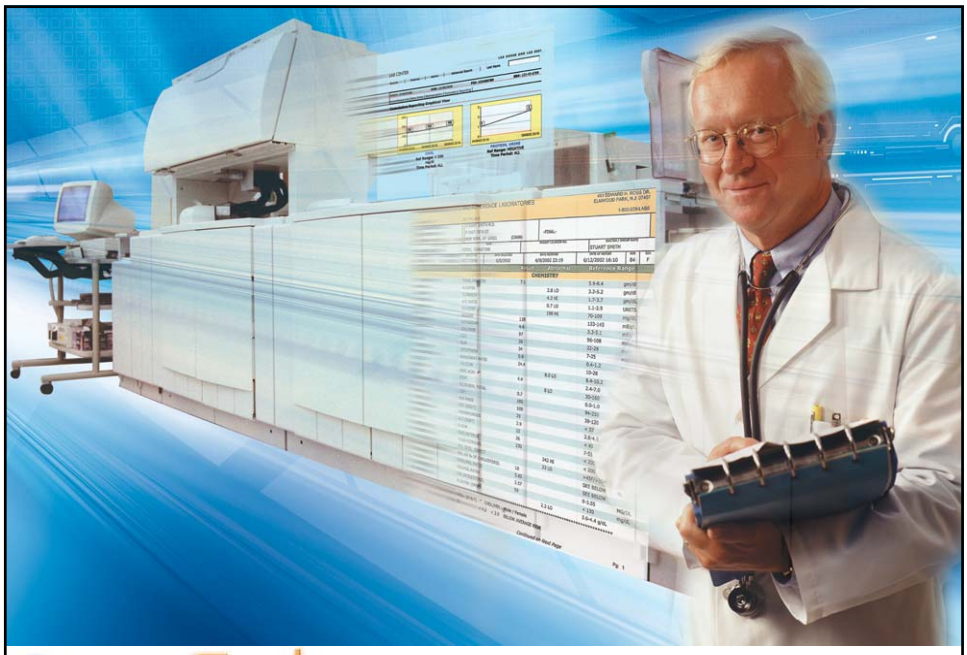

PSIMedica
APPLICATIONS
CURRENT DATA SOURCES
MMS Server
Eligibility
Hospital Claims
Pharmacy Data
Lab Results
Medical Claims
Profiling
Clinical Efficiency
PSIMedica Quality Indicators (PQI's)
No One Pays For Quality
Management
Abuse Reporting
Administrative Data
• Demographics
• Cost Control
• Utilization
Outcomes Research
Market Research
2001


Care evolve
Better Healthcare Through Better Communication .com
Patient Education
Secure Messaging
Health News
Financial Services
CME Courses
Web Site Design
Computer Hardware
Claims Eligibility
Claims Processing
Consultation
Personal Services
Medical Staffing
Office Supplies
Disease Management
Lab Results
Medical Supplies
Prescriptions
Immunization Program
Office Scheduling
Patient Referrals
Patient Care Record
Email
Hello! And Welcome to Care Evolve
LOGIN
Username:
Password:
ENTER
Contact Us
2000

CareEvolve

- Web-based, physician application that includes office productivity tools and provides on-line clinical ordering and reporting, laboratory and radiology
- Clients include:
  - 40 Hospital Systems or Laboratories, representing nearly 175 facilities
  - Over 6,700 physicians representing more than 215,000 patients
  - 500M reports delivered to date
- Growing connectivity network poised to deliver web based patient management solutions

2009



CareEvolve

2009

Current Status - BioReference/GenPath

- Over 3,500 Physician users
- Patient Service Centers – Live on orders and results
- GenPath – HTML and PDF reporting
- 6 years online results
- Advanced Features to provide individual and group data analysis

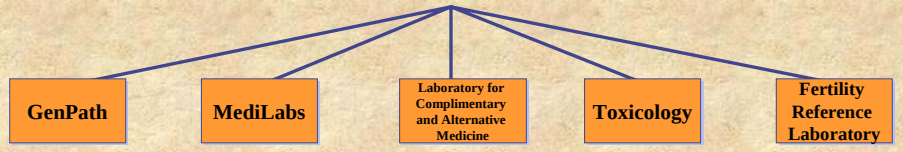
CareEvolve

2009

BRLI Capabilities

BRLI

Automated, High Volume, Clinical Testing Facilities with Specialty Boutiques



GenPath
- Cancer Pathology & Cytology diagnostic services
- Genomics testing
- Full service Oncology laboratory

MediLabs
- Institutional testing services
- Correctional facilities
- Sub acute, nursing facility services

Laboratory for Complimentary and Alternative Medicine
- Heavy Metal, Amino Acid, and Vitamin Testing
- Alternative Medicine

Toxicology
- Drug toxicology
- Psychiatric & substance abuse
- Corporate human resource services

Fertility Reference Laboratory
- Andrology Fertility and Testing
- Hormone testing

2001

BRLI Capabilities 2009

Franchises

Each Unit with its own Marketing, Testing and Identity

BRLI

Regional Clinical Laboratory
- Automated
- High Volume
- Physician Office

Correctional Healthcare
- Routine testing
- Formularies
- Regulatory Reporting
- Informatics
- HIV, HepC and other molecular tests

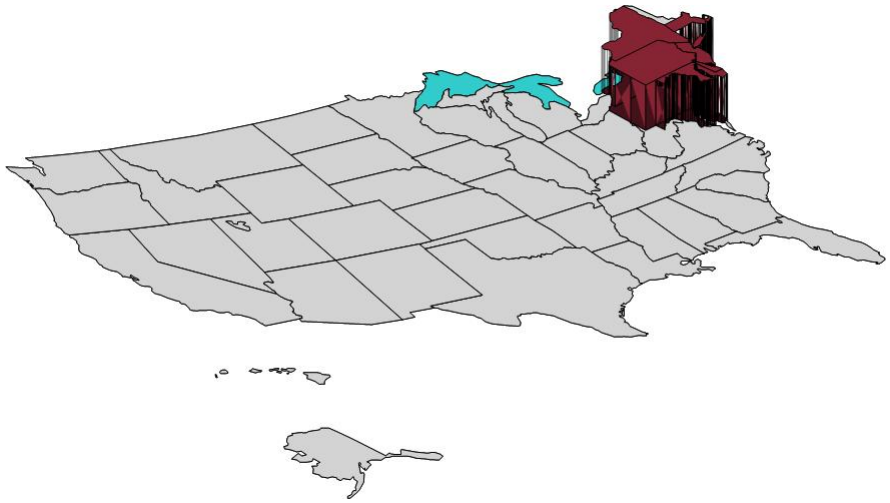
GeneDx
- DNA Sequencing
- aCGH Array testing
- NextGen Sequencing

GenPath
- Cancer Pathology &
- Genomics testing
- Full service Oncology laboratory

Women's Health
- Thin-Prep, Image Directed Paps
- HPV, CT/ GC
- STI Testing
- Molecular testing

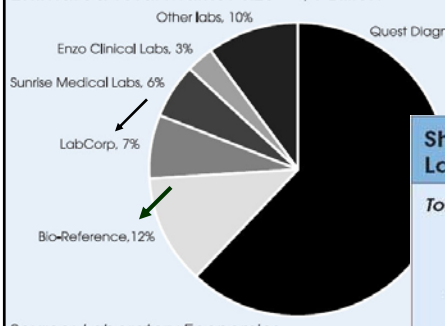
2009

The Regional Laboratory



Share of Physician Office Market in the New York City Area

Estimated Total Market Size = $1 Billion

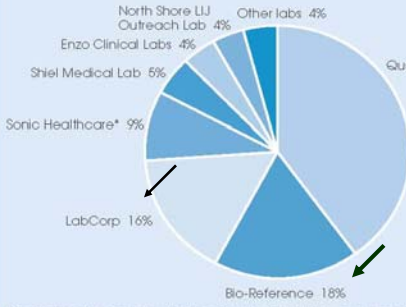


Source: *Laboratory Economics*

As of October 1, 2006

Share of the Physician Office Market for Lab Services in NYC Area

Total Estimated Market Size=$1.1 Billion



*Sonic Healthcare includes Sunrise Medical Labs and American Clinical Service

Source: *Laboratory Economics*

As of June 1, 2008

2009

The Regional Laboratory

As a Regional Laboratory, BRLI has an infrastructure second to none.

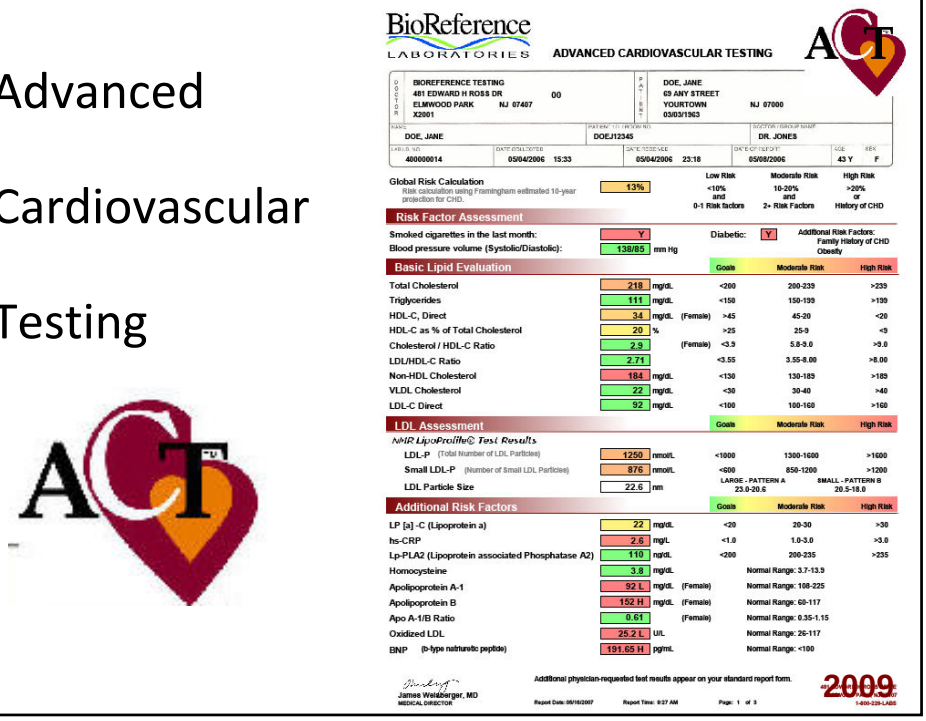
- **"Feet on the Street"**
- **Existing Customer base and Infrastructure**
- **Provider of all of the testing, services and support of the national laboratories with the focused attention of a local regional laboratory**
- **Superior technology and connectivity solutions**
- **Inclusion in most managed care plans**

2009

Advanced

Cardiovascular

Testing



BioReference LABORATORIES

ADVANCED CARDIOVASCULAR TESTING

ACT

BIOREFERENCE TESTING
481 EDWARD H ROSS DR 00
ELMWOOD PARK NJ 07407
X2001

DOE, JANE
69 ANY STREET
YOURTOWN NJ 07000
03/03/1963

NAME: DOE, JANE | PATIENT ID: DOEJ12345 | DOCTOR: DR. JONES

LABID NO: 400000014 | DATE COLLECTED: 05/04/2006 15:33 | DATE RECEIVED: 05/04/2006 23:18 | DATE OF REPORT: 05/08/2006 | AGE: 43 Y | SEX: F

Global Risk Calculation — 13%
Risk calculation using Framingham estimated 10-year projection for CHD.

Low Risk	Moderate Risk	High Risk
<10% and 0-1 Risk factors	10-20% and 2+ Risk Factors	>20% or History of CHD

Risk Factor Assessment

Smoked cigarettes in the last month: Y
Diabetic: Y
Additional Risk Factors: Family History of CHD, Obesity
Blood pressure volume (Systolic/Diastolic): 138/85 mm Hg

Basic Lipid Evaluation				Goals	Moderate Risk	High Risk
Total Cholesterol	218	mg/dL		<200	200-239	>239
Triglycerides	111	mg/dL		<150	150-199	>199
HDL-C, Direct	34	mg/dL	(Female)	>45	45-20	<20
HDL-C as % of Total Cholesterol	20	%		>25	25-9	<9
Cholesterol / HDL-C Ratio	2.9		(Female)	<3.9	5.8-9.6	>9.6
LDL/HDL-C Ratio	2.71			<3.55	3.55-8.00	>8.00
Non-HDL Cholesterol	184	mg/dL		<130	130-189	>189
VLDL Cholesterol	22	mg/dL		<30	30-40	>40
LDL-C Direct	92	mg/dL		<100	100-160	>160

LDL Assessment			Goals	Moderate Risk	High Risk
NMR LipoProfile® Test Results					
LDL-P (Total Number of LDL Particles)	1250	nmol/L	<1000	1300-1600	>1600
Small LDL-P (Number of Small LDL Particles)	876	nmol/L	<600	850-1200	>1200
LDL Particle Size	22.6	nm	LARGE - PATTERN A 23.0-20.6		SMALL - PATTERN B 20.5-18.0

Additional Risk Factors				Goals	Moderate Risk	High Risk
LP [a] -C (Lipoprotein a)	22	mg/dL		<20	20-30	>30
hs-CRP	2.6	mg/L		<1.0	1.0-3.0	>3.0
Lp-PLA2 (Lipoprotein associated Phosphatase A2)	110	ng/dL		<200	200-235	>235
Homocysteine	3.8	mg/dL		Normal Range: 3.7-13.9		
Apolipoprotein A-1	92 L	mg/dL	(Female)	Normal Range: 108-225		
Apolipoprotein B	152 H	mg/dL	(Female)	Normal Range: 60-117		
Apo A-1/B Ratio	0.61		(Female)	Normal Range: 0.35-1.15		
Oxidized LDL	25.2 L	U/L		Normal Range: 26-117		
BNP (b-type natriuretic peptide)	191.65 H	pg/mL		Normal Range: <100		

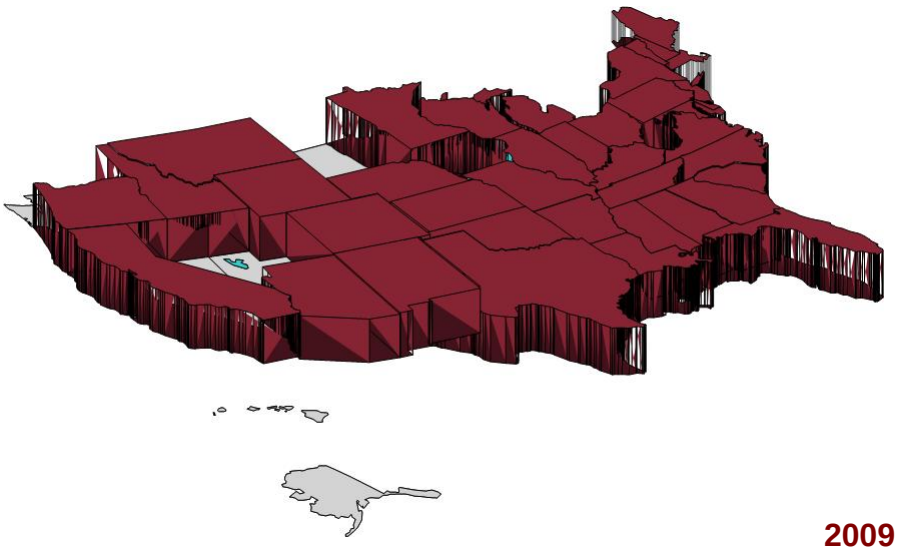
James Weisberger, MD
MEDICAL DIRECTOR

Additional physician-requested test results appear on your standard report form.

Report Date: 05/10/2007 Report Time: 8:27 AM Page: 1 of 3

2009

Correctional Healthcare



2009

Correctional Healthcare

- Established presence in NY, NJ, PA, MD, KS, WI, VT, ME, MO, NH, AL, DE, NC, FL, GA, SC, AZ, IL, MA, AR, NM, ID, MN, KY, OH, MI, CA, LA, MO, CO, DC, OK, OR, IN, NE, TN, WY, TX and VA (including prisons and jails);
- Contracts with the two largest (PHS and CMS) and four of the five largest national correctional healthcare services companies as well as regional companies;
- Highly trained staff that works exclusively in correctional healthcare throughout the country; providing specialized services through customized solutions;
- Valuable Informatics solutions (EMR - ChartEvolve, Reporting - CareEvolve, Population management - PSIMedica) provide value-added laboratory differentiation.

2009

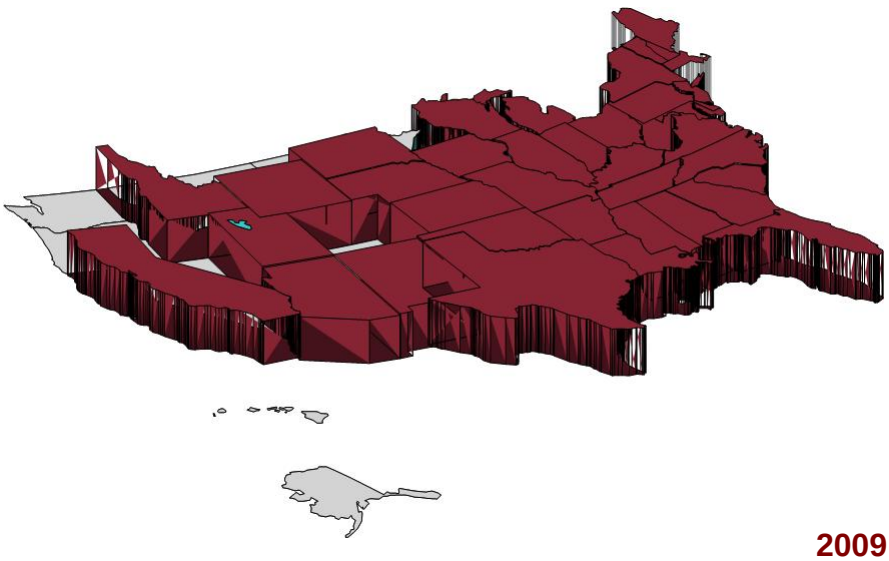
Onco-Pathology Services

GenPath – ***State of the Art Testing Facilities***

Onco-Pathology Services		***Testing Modalities***
HEMATOLOGY/ ONCOLOGY • Leukemia, Lymphoma, & Myelodysplastic Syndromes	Diagnostic, Prognostic & Therapeutic Monitoring of Disease	***Morphology***
BREAST CANCER • Pathology Tumor Analysis	Benign or Malignant • Unknown Primary • Undifferentiated Tumor • Microscopic Disease Staging	***Immunohistochemistry***
GASTROENTEROLOGY	Pathologic Diagnosis & Prognosis of Upper & Lower GI Malignancies	***Flow Cytometry***
UROLOGY	Early Detection, Diagnostic & Prognostic Testing for Bladder & Prostate Cancer	***Cytogenetics***
OB/GYN	Early Detection, Diagnostic & Prognostic Testing Incorporating Latest Pap Smear Technology; ThinPrep & HPV Typing	***Fluorescence In Situ Hybridization (F.I.S.H)***

2001

GENPATH



2009

The GenPath Advantage

- Superior Professional Service & Support
- Foremost Experts selected for Scientific Advisory Board
- Cutting Edge Technology
- Superior Sales and Marketing
- Patient Centric / Medically Appropriate

2009

Foremost Experts Serve as Scientific Advisory Board Members, Consultants or Advisors

- John Bennett, MD - U of Rochester
- Ayalew Tefferi, MD - Mayo Clinic
- Stephen D. Nimer, MD – Memorial Sloan-Kettering
- Paul Rothberg, PhD - U of Rochester
- Rajendra Damle, PhD - NYU Medical Center
- Barry Maron, MD, U of Minnesota
- Wendy Chung, MD PhD – Columbia University
- Mathew Maurer, MD - Columbia University
- David A. Baker, MD – State U of New York, Stony Brook
- Jeffrey Gilbert, MD - Montefiore/Albert Einstein Medical Center

MAYO CLINIC

Oligonucleotide Array CGH Studies In Myeloproliferative Neoplasms: Comparison With Conventional Cytogenetic Analysis and *JAK2*V617F mutational status

Ayalew Tefferi, MD[1], Shireen Sirhan, MD[1], Yi Sun, PhD[2], Terra Lasho, MT(ASCP)[1], Christy M. Finke[1], James Weisberger, MD[2,3], Sherri Bale, PhD[4], John Compton, PhD[4], Charles A. LeDuc, PhD[5], Animesh Pardanani, MD, PhD[1], Erik C. Thorland, PhD[1], Yuriy Shevchenko PhD[4], Marc Grodman, MD[2,5], Wendy K. Chung, MD, PhD[5]

[1]Mayo Clinic, Rochester, MN, [2]BioReference Laboratories, Elmwood Park, NJ, [3]GenPath, Elmwood Park, NJ, [4]GeneDx, Gaithersburg, MD, [5]Columbia University, New York, NY

Background

- Conventional cytogenetic studies in myeloproliferative neoplasms (MPNs) have provided pathogenetic, diagnostic and prognostic information and in certain instances guide therapeutic decisions. It is therefore reasonable to hypothesize that a higher resolution examination of chromosomes might reveal additional changes that are scientifically as well as clinically relevant.

Methods

- Comparative genomic hybridization (CGH) was performed on archived DNA from peripheral blood granulocytes with a gender matched normal control using oligoarrays with either 44,000 or 105,000 oligonucleotides. Data were analyzed with CGH Analytics (Agilent). Copy number changes were considered significant (CNCs) if they were defined by 4 or more adjacent oligonucleotides spanning at least 150,000 base pairs, contained at least one gene, and were not identified in the Database of Genomic Variants. The study population was retrospectively selected based on availability of study sample and presence of a World Health Organization-defined diagnosis of *BCR-ABL*-negative classic MPN: primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocythemia (ET), post-ET MF and post-PV MF.

Results

a) Patients:

- Peripheral blood-derived granulocyte DNA from 80 patients (median age 56 years, range 18-89; 53 males) with classic *BCR-ABL*-negative MPNs were studied: 32 with PMF, 26 with PV, 13 with ET, 6 with post-ET MF and 3 with post-PV MF. Samples for array CGH study were collected at a median of 25 months (range, 0-338) from diagnosis and 37 (52%) of 71 evaluable patients had received treatment. Median (range) values at time of sample accrual were hemoglobin level 13.3 g/dL (transfusion dependent-18.2), leukocyte count 9.3 x 10^9/L (3.3-133), and platelet count 403 x 10^9/L (49-1715). Cytogenetic information, collected at variable times before the current study, was available in 57 patients. Twelve healthy volunteers were used as controls.

b) Array CGH results for all 80 study patients (Table 1):

- Array CGH revealed CNCs in 28 (35%) cases among the 80 study patients and in none of the 12 normal controls. The percentage of patients with CNCs was 44% for PMF, 35% for PV and 15% for ET. In addition, 2 of 6 patients with post-ET MF and 1 of 2 patients with post-PV MF displayed CNCs.

c) Comparison of array CGH and *JAK2*V617F mutational status in 60 informative patients:

- Sixty patients had information on *JAK2*V617F mutational status: 25 PMF, 18 PV, 13 ET, and 4 post-ET/PV MF. The mutation was detected in 43 (72%) cases including all 18 (100%) PV cases, 17 (68%) of 25 PMF cases, and 5 (39%) of 13 ET cases. Among the 38 patients with either PMF or ET, CNCs were more frequently detected in the presence of *JAK2*V617F (68% vs. 40%; p=0.05).

d) Comparison of array CGH and karyotype in 62 cases with cytogenetic studies performed at any time prior to array CGH study (Table 2):

- Cytogenetic studies were performed either at diagnosis or within 1 year of array CGH in 62 patients (25 PMF, 21 PV, 11 ET, 5 post-ET/PV MF); the results were abnormal in 10 (16%) cases. Array CGH revealed CNCs in 22 (36%) patients including 5 (50%) with abnormal and 17 (33%) with normal cytogenetic results. However, all 21 patients with PV and 11 with ET displayed normal cytogenetics despite the presence of CNCs in 29%, 33%, respectively. In PMF, the respective rates of CNCs and abnormal cytogenetics were 44% and 28%.

e) Comparison of array CGH and karyotype in 43 cases with cytogenetic studies performed within any time of array CGH study:

- Cytogenetic studies were performed within 1 year of the array CGH study in 43 patients (18 PMF, 15 PV, 6 ET, 4 post-ET/PV MF); the results were abnormal in 6 (14%) cases and normal in 37. Array CGH revealed CNCs in 16 (37%) patients including 4 (67%) with abnormal and 12 (32%) with normal cytogenetic results. However, all 15 patients with PV and 6 with ET displayed normal cytogenetics despite the presence of CNCs in 27% and 33%, respectively. In PMF, the respective rates of CNCs and abnormal cytogenetics were 44% and 28%.

Table 1

	No. of patients with CNCs (%; "n" evaluable)	No. of patients with CNCs (%; "n" evaluable)	No. of patients with CNCs (%; "n" evaluable)
All patients	28 (35%; n=80)	10 (16%; n=62)	43 (72%; n=60)
PMF only	15 (44%; n=32)	9 (36%; n=25)	17 (68%; n=25)
PV only	9 (35%; n=26)	0 (0%; n=0)	18 (100%; n=18)
ET only	2 (15%; n=13)	0 (0; n=11)	5 (39%; n=13)
Post-ET/PV PMF (n=9)	3 (33%; n=9)	1 (20%; n=5)	3 (75%; n=4)

Table 2

	No. Of Patients with CNCs (%)
All patients (n=62)	22 (36%)
Patients with normal cytogenetics (n=52)	17 (33%)
Patients with abnormal cytogenetics (n=10)	5 (50%)
All PMF patients (n=25)	12 (48%)
PMF patients with normal cytogenetics (n=16)	8 (50%)
PMF patients with abnormal cytogenetics (n=9)	4 (44%)
All PV patients (n=21)	6 (29%)
PV patients with normal cytogenetics (n=21)	6 (29%)
PV patients with normal cytogenetics (n=0)	N/A
All ET patients (n=11)	2 (18%)
ET patients with normal cytogenetics (n=11)	2 (18%)
ET patients with abnormal cytogenetics (n=0)	N/A

Conclusions

1) **In PV and ET, oligonucleotide array CGH is superior to bone marrow cytogenetic analysis in detecting genomic aberrations. Furthermore, in these two disorders, array CGH is more likely to detect genomic changes in the presence of *JAK2*V617F.**
2) **Oligonucleotide array CGH in PMF discloses the occurrence of genomic losses that accompany translocations, which are assumed to be balanced by cytogenetic analysis.**
3) **Prospective studies with concomitant assessment of array CGH and cytogenetic studies are required to clarify the diagnostic and prognostic value of the former in comparison to the latter.**
4) **The non-trivial rate of detecting array CGH-apparent genomic changes in PV and ET warrants further studies to examine its prognostic value.**

2009

GENPATH

Cutting Edge Technology

Utility of oligonucleotide array comparative genomic hybridization to identify cryptic copy number alterations in myelodysplastic syndromes

Wendy Chung, James Weisberger, Pauline Brenholz, Stephanie Warren, Swaroop Aradhya, Charles LeDuc, Marc Grodman, Anwar Iqbal, John Bennett

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematological neoplasms characterized by peripheral cytopenias due to ineffective hematopoiesis and significant cytologic atypia in one or more of the myeloid lineages. There is a variable risk of progression to acute myeloid leukemia, which is dependent on the blast count and certain recurrent cytogenetic abnormalities. Cytogenetic characterization is important in both diagnosis and prognosis, but can be of limited value in many cases because of the low frequency of karyotypic abnormalities in lower-risk subtypes.

2009

GENPATH

Cutting

Edge

Technology

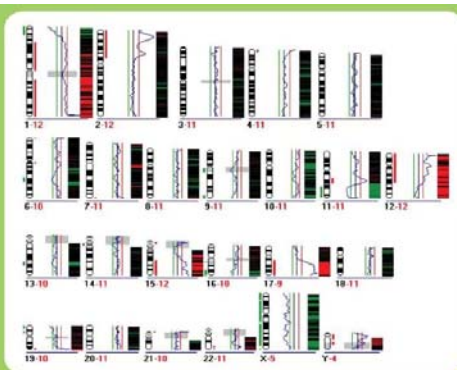


Figure 1: A molecular karyotype showing gains and losses across the genome. Gains are depicted in green and losses in red.

Molecular Karyotyping: Beyond conventional cytogenetics

- Conventional cytogenetics is an integral tool in the detection of chromosomal anomalies such as deletions, duplications and aneuploidies.
- However, DNA amplifications, double minutes and homogeneously staining regions cannot always be accurately localized to specific chromosomal bands.1 Also, in the case of culture failure or no cell growth, conventional karyotyping cannot be performed.
- Array CGH is a comparative genomic hybridization methodology in which a large number of nucleic acid probes are used to detect chromosomal abnormalities in a patient sample.

2009

GENPATH

Personalized Medicine Requisition Form
Cutting Edge Technology

PERSONALIZED MEDICINE REQUISITION Form #

ALL INSURANCES
RELATIONSHIP TO SUBSCRIBER ☐ CHILD ☐ SELF ☐ SPOUSE ☐ OTHER _____

PHYSICIAN'S SIGNATURE (REQUIRED FOR MEDICAID)

SPECIMEN INFORMATION

SURGICAL # | PATIENT I.D. / ROOM NO.

Collection Date: _____ Time: _____ Multiple ☐ Y ☐ N

☐ Blood ☐ Bone Marrow ☐ Fresh Tissue-Body Site _____

ENTRIES IN THIS BOX WILL APPEAR ON REPORT

CLINICAL INFORMATION

TESTS / PANELS			SAMPLE REQUIREMENTS	
☐ 5288-6	**KRAS (Cetuximab, Gefitinib, Erlotinib, Panitumumab)** KRAS mutations in tumor tissue are associated with unfavorable prognosis in cancer patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI).		FFPE*	Block
☐ 5295-1	**EGFR (Cetuximab, Gefitinib, Erlotinib, Panitumumab)** Mutations in the EGFR gene affect response rates of patients on EGFR TKI therapy.		FFPE*	Block
☐ 5322-3	**BRAF (Cetuximab, Gefitinib, Erlotinib, Panitumumab)** BRAF mutations in colorectal cancer cause resistance to anti-EGFR therapy.		FFPE*	Block
☐ 6290-1	**ABL Kinase (Imatinib)** Imatinib resistance can be attributed to a change in the BCR/ABL mutation status.		Whole Blood/Bone Marrow	EDTA
☐ 5179-7	**C-KIT (Imatinib)** C-kit mutations affect the efficacy of Imatinib and cause failure of therapy in most patients.		Whole Blood	EDTA
☐ 5183-9	**UGT1A1 (Irinotecan, Leucovorin, 5-FU)** Mutations in the UGT1A1 gene impair production of the enzyme that metabolizes chemotherapeutic drugs.		Whole Blood	EDTA
☐ 6285-1	**DPD (5-FU)** Mutations in the DPD gene are known to cause abnormal metabolism of 5FU causing drug toxicities.		Whole Blood	EDTA
☐ 5287-8	**CYP2D6 (Tamoxifen)** Patients with certain CYP2D6 gene alleles have significantly impaired ability to metabolize tamoxifen resulting in treatment-related toxicity.		Whole Blood	EDTA
☐ 6261-2	**CYP2C9, VKORC1 (Warfarin)** Warfarin metabolism is dependent on a patient's genotype which in turn affects their response to therapy.		Whole Blood	EDTA
Coagulation Risk Assessment Panels:				
☐ 5993-1	**Hyperactive Coagulation Panel** Measurement of activation markers used to assess any increase in a patient's tendency to clot.		Frozen Plasma*	3 Blue citrate
☐ 5997-2	**Bleeding Diathesis Evaluation** Assessment of coagulation factors in patients with possible inherited or acquired bleeding disorders.		Frozen Plasma* and Whole Blood	3 Blue citrate 1 EDTA

2009

GenPath Sales Team:
Superior Sales and Marketing

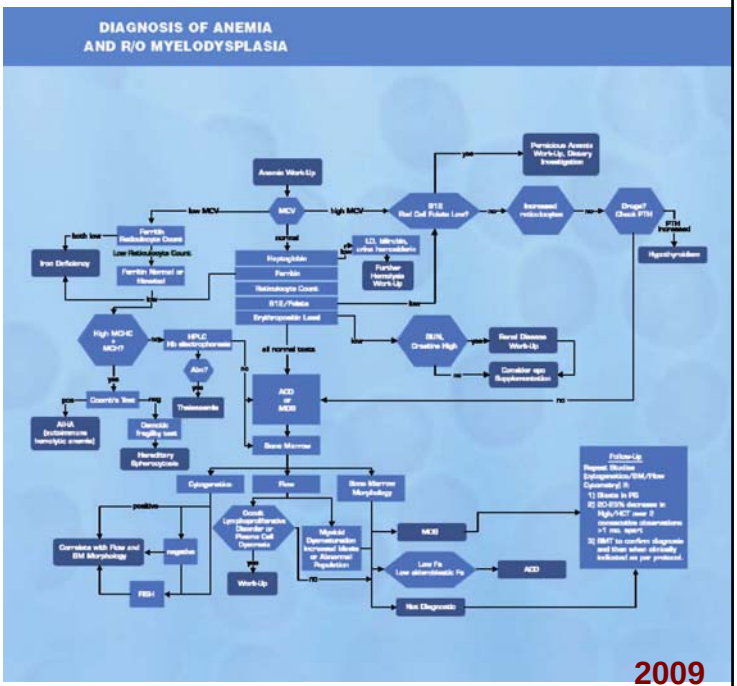
- GenPath Leadership Brochure
- GenPath Diagnostic Guidelines
- GenPath Anatomic Pathology Services
- GenPartners Program
- K-RAS Testing
- Coagulation Testing
- Personalized Medicine

2009

Patient Centric / Medically Appropriate

Physician Testing Algorithm

MDS



2009

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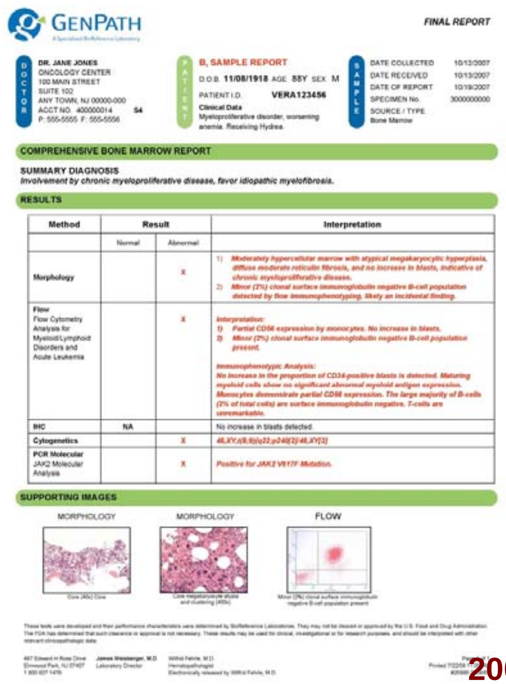
Personalized Reporting



GENPATH

FINAL REPORT

DOCTOR
DR. JANE JONES
ONCOLOGY CENTER
100 MAIN STREET
SUITE 102
ANY TOWN, NJ 00000-000
ACCT NO. 400000014 S4
P: 555-5555 F: 555-5556

PATIENT
B, SAMPLE REPORT
D.O.B. 11/08/1918 AGE 88Y SEX M
PATIENT I.D. VERA123456
Clinical Data
Myeloproliferative disorder, worsening anemia. Receiving Hydrea.

SAMPLE
DATE COLLECTED 10/12/2007
DATE RECEIVED 10/13/2007
DATE OF REPORT 10/19/2007
SPECIMEN No. 3000000000
SOURCE / TYPE
Bone Marrow

COMPREHENSIVE BONE MARROW REPORT

SUMMARY DIAGNOSIS
Involvement by chronic myeloproliferative disease, favor idiopathic myelofibrosis.

RESULTS

Method	Result		Interpretation
	Normal	Abnormal	
Morphology		X	1) *Moderately hypercellular marrow with atypical megakaryocytic hyperplasia, diffuse moderate reticulin fibrosis, and no increase in blasts, indicative of chronic myeloproliferative disease.* 2) *Minor (2%) clonal surface immunoglobulin negative B-cell population detected by flow immunophenotyping, likely an incidental finding.*
Flow Flow Cytometry Analysis for Myeloid/Lymphoid Disorders and Acute Leukemia		X	*Interpretation:* 1) *Partial CD56 expression by monocytes. No increase in blasts.* 2) *Minor (2%) clonal surface immunoglobulin negative B-cell population present.* *Immunophenotypic Analysis:* *No increase in the proportion of CD34-positive blasts is detected. Maturing myeloid cells show no significant abnormal myeloid antigen expression. Monocytes demonstrate partial CD56 expression. The large majority of B-cells (2% of total cells) are surface immunoglobulin negative. T-cells are unremarkable.*
IHC	NA		No increase in blasts detected.
Cytogenetics		X	*46,XY,t(8;9)(q22;p24)[2]/46,XY[3]*
PCR Molecular JAK2 Molecular Analysis		X	*Positive for JAK2 V617F Mutation.*

SUPPORTING IMAGES

MORPHOLOGY

MORPHOLOGY

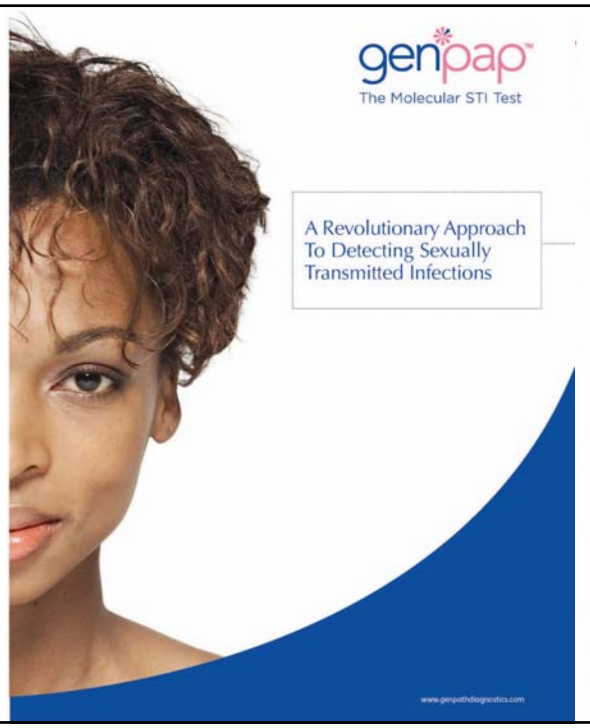
FLOW

Patient Centric

/ Medically Appropriate

2009

Women's Health Initiative

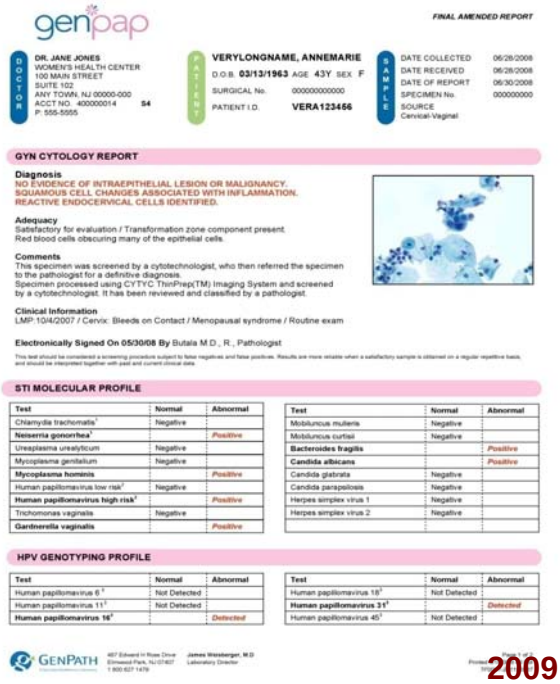


Patient Centric

/ Medically Appropriate

2009

- Women's
- Health
- Initiative
  - Patient Centric
  - / Medically
  - Appropriate



genpap

FINAL AMENDED REPORT

DOCTOR: DR. JANE JONES, WOMEN'S HEALTH CENTER, 100 MAIN STREET, SUITE 102, ANY TOWN, NJ 00000-000, ACCT NO. 400000014 54, P: 555-5555

PATIENT: VERYLONGNAME, ANNEMARIE, D.O.B. 03/13/1963 AGE 43Y SEX F, SURGICAL No. 000000000000, PATIENT I.D. VERA123456

SAMPLE: DATE COLLECTED 06/28/2008, DATE RECEIVED 06/28/2008, DATE OF REPORT 06/30/2008, SPECIMEN No. 000000000, SOURCE Cervical-Vaginal

GYN CYTOLOGY REPORT

Diagnosis
NO EVIDENCE OF INTRAEPITHELIAL LESION OR MALIGNANCY.
SQUAMOUS CELL CHANGES ASSOCIATED WITH INFLAMMATION.
REACTIVE ENDOCERVICAL CELLS IDENTIFIED.

Adequacy
Satisfactory for evaluation / Transformation zone component present.
Red blood cells obscuring many of the epithelial cells.

Comments
This specimen was screened by a cytotechnologist, who then referred the specimen to the pathologist for a definitive diagnosis.
Specimen processed using CYTYC ThinPrep(TM) Imaging System and screened by a cytotechnologist. It has been reviewed and classified by a pathologist.

Clinical Information
LMP: 10/4/2007 / Cervix: Bleeds on Contact / Menopausal syndrome / Routine exam

Electronically Signed On 05/30/08 By Butala M.D., R., Pathologist

This test should be considered a screening procedure subject to false negatives and false positives. Results are more reliable when a satisfactory sample is obtained on a regular repetitive basis, and should be interpreted together with past and current clinical data.

STI MOLECULAR PROFILE

Test	Normal	Abnormal
Chlamydia trachomatis[1]	Negative	
Neisseria gonorrhea[1]		Positive
Ureaplasma urealyticum	Negative	
Mycoplasma genitalium	Negative	
Mycoplasma hominis		Positive
Human papillomavirus low risk[2]	Negative	
Human papillomavirus high risk[2]		Positive
Trichomonas vaginalis	Negative	
Gardnerella vaginalis		Positive

Test	Normal	Abnormal
Mobiluncus mulieris	Negative	
Mobiluncus curtisii	Negative	
Bacteroides fragilis		Positive
Candida albicans		Positive
Candida glabrata	Negative	
Candida parapsilosis	Negative	
Herpes simplex virus 1	Negative	
Herpes simplex virus 2	Negative	

HPV GENOTYPING PROFILE

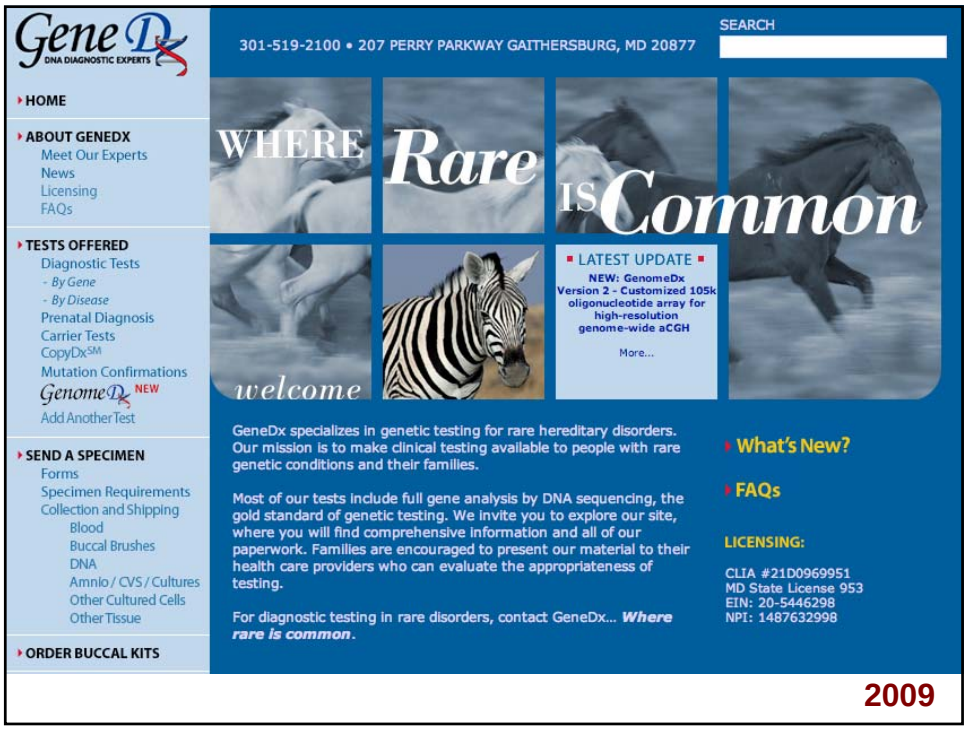
Test	Normal	Abnormal
Human papillomavirus 6[1]	Not Detected	
Human papillomavirus 11[1]	Not Detected	
Human papillomavirus 16[1]		Detected

Test	Normal	Abnormal
Human papillomavirus 18[1]	Not Detected	
Human papillomavirus 31[1]		Detected
Human papillomavirus 45[1]	Not Detected	

GENPATH 407 Edward H Ross Drive Elmwood Park, NJ 07407 1 800 627 1479 James Weisberger, M.D. Laboratory Director

Page 1 of 1

2009



GeneDx DNA DIAGNOSTIC EXPERTS

301-519-2100 • 207 PERRY PARKWAY GAITHERSBURG, MD 20877

SEARCH

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Meet Our Experts
News
Licensing
FAQs

TESTS OFFERED
Diagnostic Tests
- By Gene
- By Disease
Prenatal Diagnosis
Carrier Tests
CopyDx℠
Mutation Confirmations
GenomeDx NEW
Add Another Test

SEND A SPECIMEN
Forms
Specimen Requirements
Collection and Shipping
Blood
Buccal Brushes
DNA
Amnio / CVS / Cultures
Other Cultured Cells
Other Tissue

ORDER BUCCAL KITS

WHERE Rare IS Common

welcome

LATEST UPDATE
NEW: GenomeDx Version 2 - Customized 105k oligonucleotide array for high-resolution genome-wide aCGH
More...

GeneDx specializes in genetic testing for rare hereditary disorders. Our mission is to make clinical testing available to people with rare genetic conditions and their families.

Most of our tests include full gene analysis by DNA sequencing, the gold standard of genetic testing. We invite you to explore our site, where you will find comprehensive information and all of our paperwork. Families are encouraged to present our material to their health care providers who can evaluate the appropriateness of testing.

For diagnostic testing in rare disorders, contact GeneDx... ***Where rare is common***.

What's New?

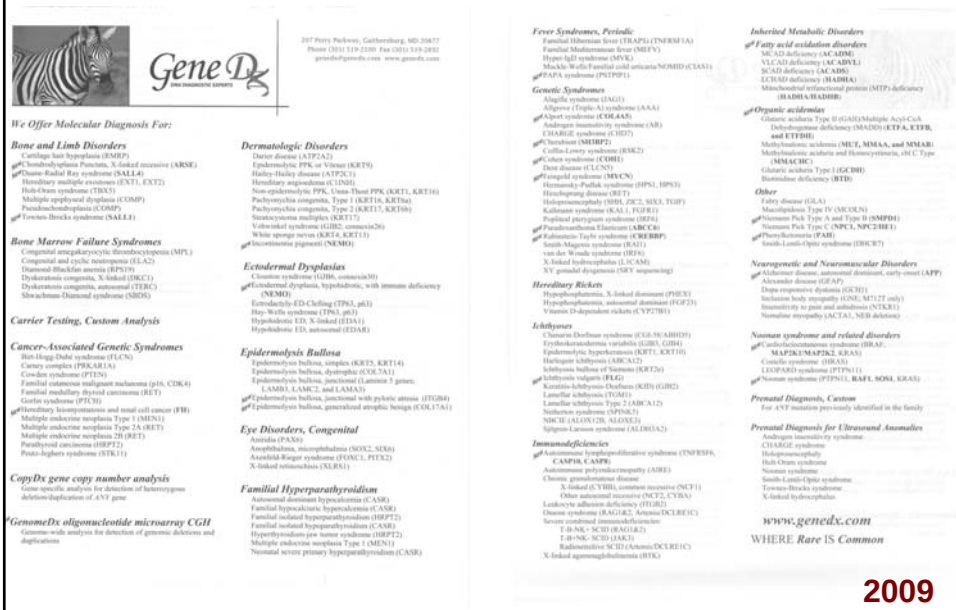
FAQs

LICENSING:

CLIA #21D0969951
MD State License 953
EIN: 20-5446298
NPI: 1487632998

2009

GeneDx Current Test Offerings



We Offer Molecular Diagnosis For:

Bone and Limb Disorders
Cartilage hair hypoplasia (RMRP)
Chondrodysplasia Punctata, X-linked recessive (ARSE)
Dyane-Radial Ray syndrome (SALL4)
Hereditary multiple exostoses (EXT1, EXT2)
Holt-Oram syndrome (TBX5)
Multiple epiphyseal dysplasia (COMP)
Pseudoachondroplasia (COMP)
Townes-Brocks syndrome (SALL1)

Bone Marrow Failure Syndromes
Congenital amegakaryocytic thrombocytopenia (MPL)
Congenital and cyclic neutropenia (ELA2)
Diamond-Blackfan anemia (RPS19)
Dyskeratosis congenita, X-linked (DKC1)
Dyskeratosis congenita, autosomal (TERC)
Shwachman-Diamond syndrome (SBDS)

Carrier Testing, Custom Analysis

Cancer-Associated Genetic Syndromes
Birt-Hogg-Dubé syndrome (FLCN)
Carney complex (PRKAR1A)
Cowden syndrome (PTEN)
Familial cutaneous malignant melanoma (p16, CDK4)
Familial medullary thyroid carcinoma (RET)
Gorlin syndrome (PTCH)
Hereditary leiomyomatosis and renal cell cancer (FH)
Multiple endocrine neoplasia Type 1 (MEN1)
Multiple endocrine neoplasia Type 2A (RET)
Multiple endocrine neoplasia 2B (RET)
Parathyroid carcinoma (HRPT2)
Peutz-Jeghers syndrome (STK11)

CopyDx gene copy number analysis
Gene-specific analysis for detection of heterozygous deletion/duplication of ANY gene

GenomeDx oligonucleotide microarray CGH
Genome-wide analysis for detection of genomic deletions and duplications

Dermatologic Disorders
Darier disease (ATP2A2)
Epidermolytic PPK or Vörner (KRT9)
Hailey-Hailey disease (ATP2C1)
Hereditary angioedema (C1INH)
Non-epidermolytic PPK, Unna-Thost PPK (KRT1, KRT16)
Pachyonychia congenita, Type 1 (KRT16, KRT6a)
Pachyonychia congenita, Type 2 (KRT17, KRT6b)
Steatocystoma multiplex (KRT17)
Vohwinkel syndrome (GJB2, connexin26)
White sponge nevus (KRT4, KRT13)
Incontinentia pigmenti (NEMO)

Ectodermal Dysplasias
Clouston syndrome (GJB6, connexin30)
Ectodermal dysplasia, hypohidrotic, with immune deficiency (NEMO)
Ectrodactyly-ED-Cleftingg (TP63, p63)
Ray-Wells syndrome (TP63, p63)
Hypohidrotic ED, X-linked (EDA1)
Hypohidrotic ED, autosomal (EDAR)

Epidermolysis Bullosa
Epidermolysis bullosa, simplex (KRT5, KRT14)
Epidermolysis bullosa, dystrophic (COL7A1)
Epidermolysis bullosa, junctional (Laminin 5 genes: LAMB3, LAMC2, and LAMA3)
Epidermolysis bullosa, junctional with pyloric atresia (ITGB4)
Epidermolysis bullosa, generalized atrophic benign (COL17A1)

Eye Disorders, Congenital
Aniridia (PAX6)
Anophthalmia, microphthalmia (SOX2, SIX6)
Axenfeld-Rieger syndrome (FOXC1, PITX2)
X-linked retinoschisis (XLRS1)

Familial Hyperparathyroidism
Autosomal dominant hypocalcemia (CASR)
Familial hypocalciuric hypercalcemia (CASR)
Familial isolated hyperparathyroidism (HRPT2)
Familial isolated hypoparathyroidism (CASR)
Hyperthyroidism-jaw tumor syndrome (HRPT2)
Multiple endocrine neoplasia Type 1 (MEN1)
Neonatal severe primary hyperparathyroidism (CASR)

Fever Syndromes, Periodic
Familial Hibernian fever (TRAPS) (TNFRSF1A)
Familial Mediterranean fever (MEFV)
Hyper-IgD syndrome (MVK)
Mackle-Wells/Familial cold urticaria/NOMID (CIAS1)
PAPA syndrome (PSTPIP1)

Genetic Syndromes
Alagille syndrome (JAG1)
Aligrove (Triple-A) syndrome (AAA)
Alport syndrome (COL4A5)
Androgen insensitivity syndrome (AR)
CHARGE syndrome (CHD7)
Cherubism (SH3BP2)
Coffin-Lowry syndrome (RSK2)
Cohen syndrome (COH1)
Dent disease (CLCN5)
Ehlersdanlos syndrome (MVCN)
Hermansky-Pudlak syndrome (HPS1, HPS3)
Hirschsprung disease (RET)
Holoprosencephaly (SHH, ZIC2, SIX3, TGIF)
Kallmann syndrome (KAL1, FGFR1)
Popliteal pterygium syndrome (IRF6)
Pseudoxanthoma Elasticum (ABCC6)
Rubinstein-Taybi syndrome (CREBBP)
Smith-Magenis syndrome (RAI1)
van der Woude syndrome (IRF6)
X-linked hydrocephalus (L1CAM)
XY gonadal dysgenesis (SRY sequencing)

Hereditary Rickets
Hypophosphatemia, X-linked dominant (PHEX)
Hypophosphatemia, autosomal dominant (FGF23)
Vitamin D-dependent rickets (CYP27B1)

Ichthyoses
Chanarin-Dorfman syndrome (CGI-58/ABHD5)
Erythrokeratodermia variabilis (GJB3, GJB4)
Epidermolytic hyperkeratosis (KRT1, KRT10)
Harlequin ichthyosis (ABCA12)
Ichthyosis bullosa of Siemens (KRT2e)
Ichthyosis vulgaris (FLG)
Keratitis-Ichthyosis-Deafness (KID) (GJB2)
Lamellar ichthyosis (TGM1)
Lamellar ichthyosis Type 2 (ABCA12)
Netherton syndrome (SPINK5)
NISCIE (ALOX12B, ALOXE3)
Sjögren-Larsson syndrome (ALDH3A2)

Immunodeficiencies
Autoimmune lymphoproliferative syndrome (TNFRSF6, CASP10, CASP8)
Autoimmune polyendocrinopathy (AIRE)
Chronic granulomatous disease
X-linked (CYBB), common recessive (NCF1)
Other autosomal recessive (NCF2, CYBA)
Leukocyte adhesion deficiency (ITGB2)
Omenn syndrome (RAG1&2, Artemis/DCLRE1C)
Severe combined immunodeficiencies:
T-B-NK- SCID (RAG1&2)
T-B+NK- SCID (JAK3)
Radiosensitive SCID (Artemis/DCLRE1C)
X-linked agammaglobulinemia (BTK)

Inherited Metabolic Disorders
Fatty acid oxidation disorders
MCAD deficiency (ACADM)
VLCAD deficiency (ACADVL)
SCAD deficiency (ACADS)
LCHAD deficiency (HADHA)
Mitochondrial trifunctional protein (MTP) deficiency (HADHA/HADHB)

Organic acidemias
Glutaric aciduria Type II (GAII)/Multiple Acyl-CoA Dehydrogenase deficiency (MADD) (ETFA, ETFB, and ETFDH)
Methylmalonic acidemia (MUT, MMAA, and MMAB)
Methylmalonic aciduria and Homocystinuria, cbl C Type (MMACHC)
Glutaric aciduria Type I (GCDH)
Biotinidase deficiency (BTD)

Other
Fabry disease (GLA)
Mucolipidosis Type IV (MCOLN)
Niemann Pick Type A and Type B (SMPD1)
Niemann Pick Type C (NPC1, NPC2/HE1)
Phenylketonuria (PAH)
Smith-Lemli-Opitz syndrome (DHCR7)

Neurogenetic and Neuromuscular Disorders
Alzheimer disease, autosomal dominant, early-onset (APP)
Alexander disease (GFAP)
Dopa-responsive dystonia (GCH1)
Inclusion body myopathy (GNE, M712T only)
Insensitivity to pain and anhidrosis (NTKR1)
Nemaline myopathy (ACTA1, NEB deletion)

Noonan syndrome and related disorders
Cardiofaciocutaneous syndrome (BRAF, MAP2K1/MAP2K2, KRAS)
Costello syndrome (HRAS)
LEOPARD syndrome (PTPN11)
Noonan syndrome (PTPN11, RAF1, SOS1, KRAS)

Prenatal Diagnosis, Custom
For ANY mutation previously identified in the family

Prenatal Diagnosis for Ultrasound Anomalies
Androgen insensitivity syndrome
CHARGE syndrome
Holoprosencephaly
Holt-Oram syndrome
Noonan syndrome
Smith-Lemli-Opitz syndrome
Townes-Brocks syndrome
X-linked hydrocephalus

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WHERE *Rare* IS *Common*

2009

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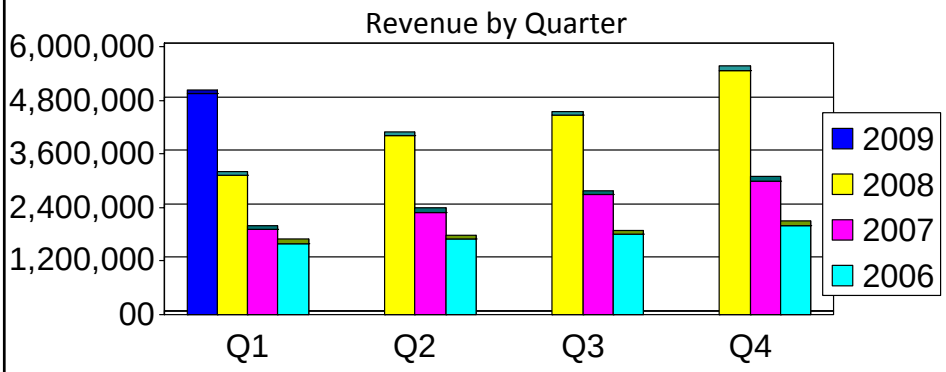
DNA DIAGNOSTIC EXPERTS
Where *Rare* is *Common*

Fiscal 2007: $9.9M

Fiscal 2008: $17M

82% increase over '07.

Q109 60% increase over Q108



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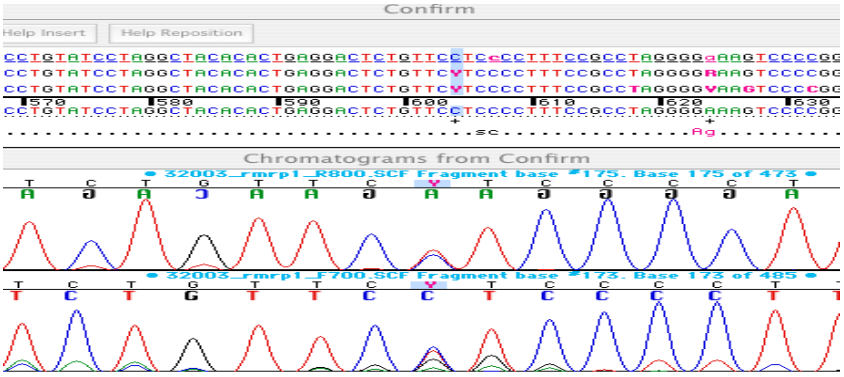
DNA DIAGNOSTIC EXPERTS
Where *Rare* is *Common*

DNA Sequencing

The GOLD Standard



Genetic Testing: The DNA Age


"All the News That's Fit to Print"

The New York Times

Late Edition

Today, sun, then clouds late, mild, high 48. Tonight, showers, low 42. Tomorrow, early clouds, a shower, then clearing, quite mild, high 50. Weather map appears on Page D2.

VOL. CLVII . . . No. 54,172 © 2007 The New York Times NEW YORK, FRIDAY, DECEMBER 28, 2007 $1.25

After DNA Diagnosis: 'Hello, 16p11.2. Are You Just Like Me?'

Samantha Napier, 14, left, and Taygen Lane, 4, share a rare genetic mutation.

THE DNA AGE
Chromosome Kinship

By AMY HARMON

The girls had never met, but they looked like sisters.

There was no missing the similarities: the flat bridge of their noses, the thin lips, the fold near the corner of their eyes. And to the families of 14-year-old Samantha Napier and 4-year-old Taygen Lane there was something else, too. In the likeness was lurking an explanation for the learning difficulties, the digestion problems, the head-banging that had troubled each of them, for so long.

Several of the adults wiped tears from their eyes. "It's like meeting family," said Jessica Houk, Samantha's older sister, who accompanied her and their mother to a Kentucky amusement park last July to greet Taygen.

But the two families are not related, and would never have met save for an unusual bond: a few months earlier, a newly available DNA test revealed that Samantha and Taygen share an identical nick in the short arm of their 16th chromosomes.

With technology that can now scan each of an individual's 46 chromosomes for minute aberrations, doctors are providing thousands of children lumped together as "autistic" or "developmentally delayed" with distinct genetic diagnoses. The symptoms, they are finding, can be traced to one of dozens of deletions or duplications of DNA that were previously hard or impossible to detect.

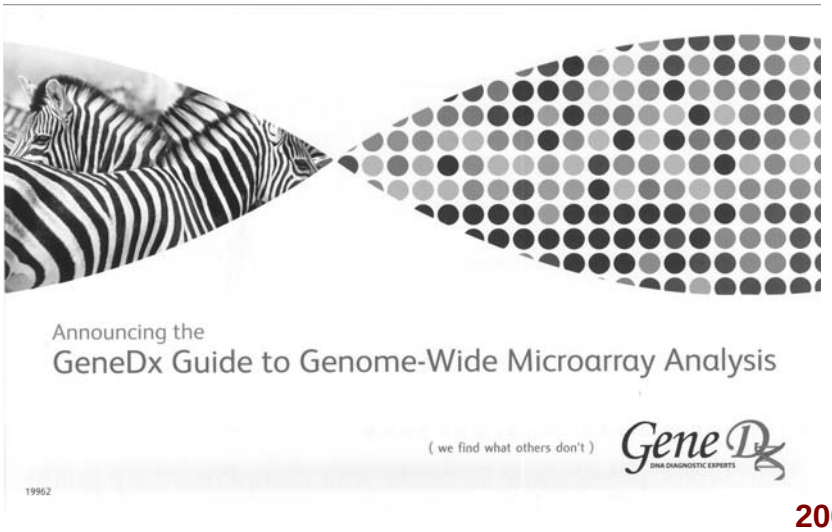
Some mutations are so rare that they are known only by their chromosomal address: Samantha and Taygen are two of only six children with the diagnosis "16p11.2."

Few of these mutations were inherited in the traditional sense, and the affected children are typically the only family member with the disorder. So, many parents are searching out strangers struck by the same genetic lightning bolt. They want solace, advice and answers to what the future might hold. From other families of children with the same chromosomal anomaly, they are seeking insight into their own. Sometimes what

Continued on Page A19

2009

GeneDx: The future of Diagnostic Testing



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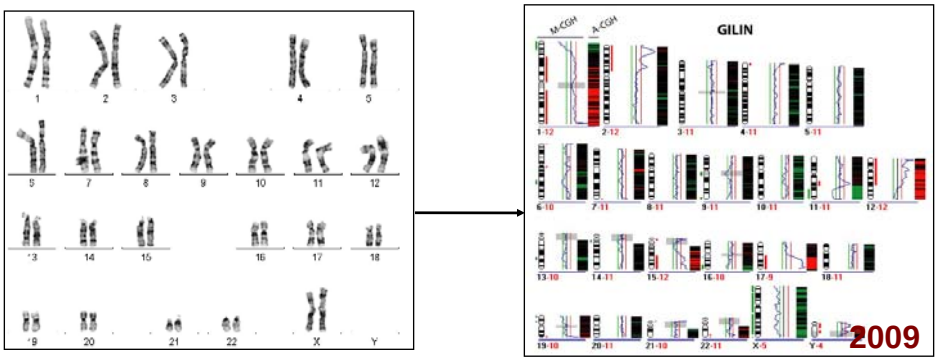
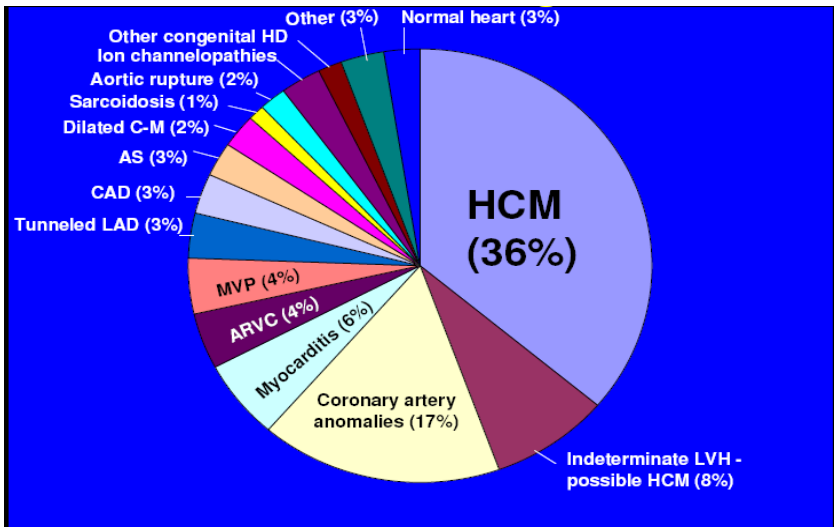
Gene Dx
DNA DIAGNOSTIC EXPERTS
Where *Rare* is *Common*

Molecular Karyotyping with Oligonucleotide Microarray



2009

Causes of Sudden Death in Young Athletes



Hypertrophic Cardiomyopathy

- Incidence of 1/500 adults, most common genetic cardiac disease
- Most common cause of sudden cardiac death in children and adolescents
- Autosomal dominantly inherited
- Family history may not be revealing
- Penetrance varies with age, hypertrophy often not apparent at least until after puberty
  - Requires serial echos
- First symptom may be sudden death

2009

Familial Hypertrophic Cardiomyopathy is Genetically Heterogeneous

Gene	Mutations	Frequency
MYH7	70	<35-50%
MYH6	1	?
MYL3	2	<1%
MYL2	8	<1%
ACTC	5	?
TNNT2	14	15-20%
TNNB	8	<1%
$TNNC_1$	1	?
TPM1	5	<5%
MYBPC3	30	>15-20%
TTN	1	?
PRKAG2	2	?

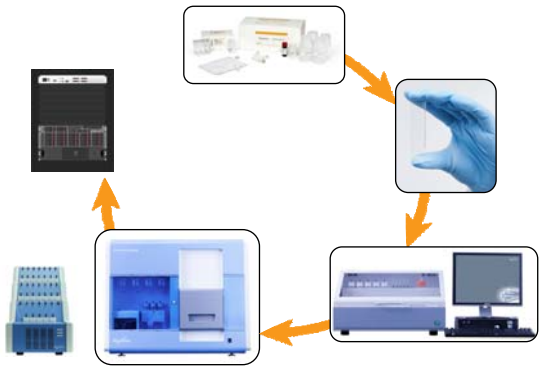
2009

Mutation Specific Prognosis

- **Troponin T (TNNT2): Highly variable, can be associated with subclinical hypertrophy with high risk of sudden cardiac death, or significant hypertrophy with low risk**
- **Cardiac myosin binding protein C (MBP-C): Late onset HCM, mild hypertrophy, good prognosis**
- **Beta Myosin Heavy Chain (MyHC): Generally early onset, poor prognosis, Generally early onset, poor prognosis**
  - Arg663His: atria fibrillation
  - Arg719Gln: heart failure
  - Arg403Gln, Arg719Trp, Arg453Cys, Arg723Gly: increased risk of sudden death (50% mortality by age 30)
  - Phe513Cys, Leu908Val, Val606Met, Gly256Glu: mild hypertrophy, low incidence of sudden death

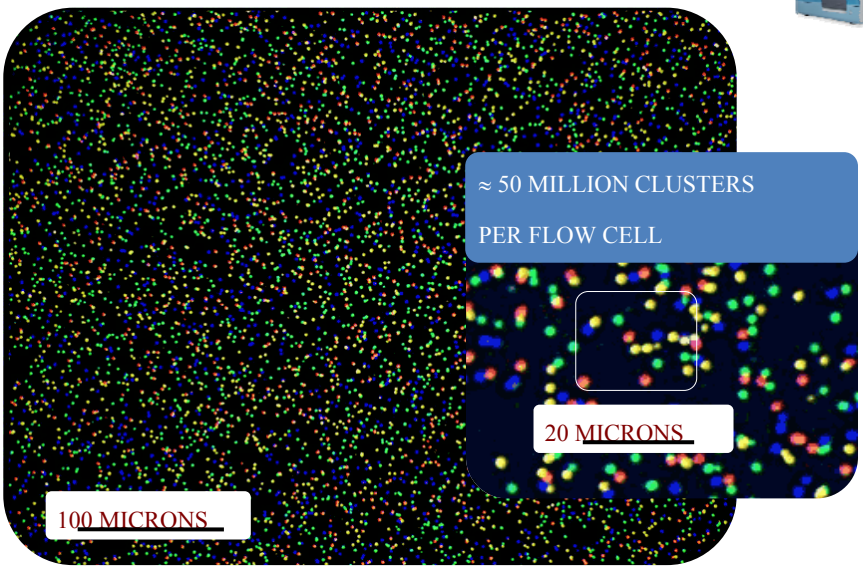
2009

What is Next Generation Sequencing ?

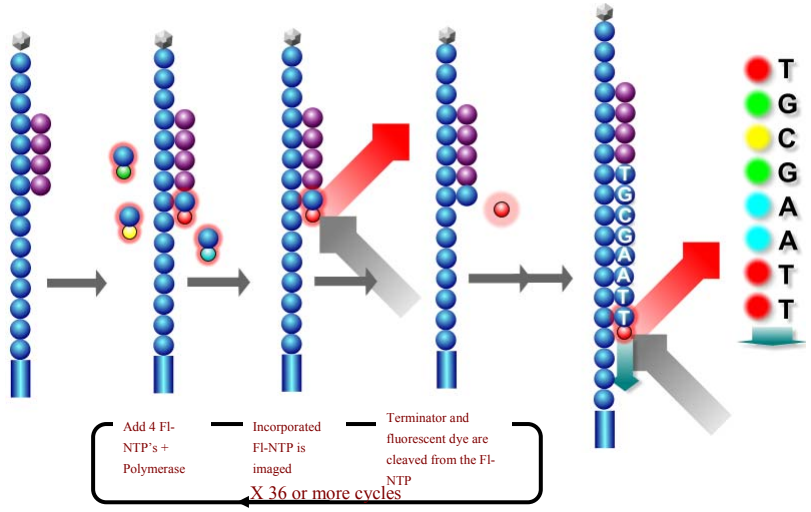


Next-Gen sequence analysis is a high-throughput technique to retrieve large amounts of sequence data in a fast, cost-effective and sensitive way.

Sequencing



Sequencing forward strand



Hypertrophic Cardiomyopathy (HCM) Panel

- 17 Genes
- Total of 172 amp icons
- Total size 77,000 BP

Conventional Sequencing:

>$17,000, several months TAT

Gene Name	Amp icons
ACTC1	10
CAV3	4
GLA	7
LAMP2	11
MTTG	1
MTTI	1
MTTK	1
MYBPC3	24
MYH7	34
MYL2	6
MYL3	4
MYLK2	9
PRKAG2	18
TNNC1	4
TNNI3	5
TNNT2	15
TPM1	14
TTR	4

GeneDx

Cardi

Isolated Hypertrophic Cardion

GeneDx accession #:	000000	Patient name:	DOE, Girl
Date specimen obtained:	01-07-2008	Date of birth:	08-31-1983
Date specimen received:	01-08-2008	Gender:	Female
Date of report:	01-21-2008	Specimen type:	Blood in ED
		Submitter ID #:	1234567

CLINICAL INDICATION: (as provided on requisition)

24-year-old female with history of syncope. Echocardiogram sho ventricle (LVIDd 4.2cm) with concentric left ventricular hypertrop PWT 16 mm). Positive family history of sudden unexplained dea and history of syncope in proband's mother.

RESULT:

Missense mutation **Arg453Cys,c1043C>T** in the **MYH7** gene Chromosome 14q12 exon 14

ABNORMAL (POSITIVE); SEE INTERPRETATION
Previously reported, known disease causing mutation

This patient has a missense mutation, altering the nucleotide C t in the MYH7 gene. This results in a change in the amino acid ar β-cardiac myosin heavy chain causing familial hypertrophic card

INTERPRETATION:

This patient has a missense mutation in the β-cardiac myosin he Mutations in *MYH7* (OMIM 160760)[1] are associated with autoso hypertrophic cardiomyopathy. Genotype-phenotype correlations been associated with a high incidence of sudden cardiac death

Familial hypertrophic cardiomyopathy is an autosomal dominant mutations in sarcomeric proteins. The disease is characterized b hypertrophy and myocardial disarray[2]. *MYH7* mutations account of hypertrophic cardiomyopathy cases[3].

RECOMMENDATION:

1. Clinical correlation between this result and the patient's pher recommended (see clinical implications below).
2. Genetic counseling is recommended to discuss the implicati
3. Mutation specific genetic testing and clinical follow-up is rec degree relatives and extended family members. Based on fa the mutation is most likely inherited from the patient's mater

CLINICAL IMPLICATIONS

Given that the patient has two major risk factors for sudden card unexplained syncope, and (2) family history of sudden cardiac d mutation (Arg453Cys) that is malignant, preventive interventions considered.[4]

GeneDx • 207 Perry Parkway • Gaithersburg, MD 20877 • Tel (301) 519-2100 • Fax (301) 519-28

GeneDx

Cardiology Genetics

Isolated Hypertrophic Cardiomyopathy Panel

GeneDx accession #:	000000	Patient name:	DOE, Girl
Date specimen obtained:	01-07-2008	Date of birth:	08-31-1983
Date specimen received:	01-08-2008	Gender:	Female
Date of report:	01-21-2008	Specimen type:	Blood in EDTA
		Submitter ID #:	1234567

Adapted from: Seidman JG, Seidman C. Cell 2001; 104: 557-67

REFERENCES:

1. Online Mendelian Inheritance in Man.
   - www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM
2. Marian AJ et al., *Annual Review of Medicine* 1995; 46:213-22
   - (PubMed: 7598456)
3. McKenna W, et al., *Europace* 2000; 2:4-14
   - http://europace.oxfordjournals.org/cgi/reprint/2/1/4.pdf
4. Watkins H et al., *N. England Journal of Medicine* 1992; 326: 1108-14
   - (PubMed: 1552912)
5. Ko YL et al. *Hum Genet.* 1996 May;97(5):585-90
   - (PubMed: 8655125)
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   - (PubMed: 12975413)
7. Greber-Platzer S et al., *J Mol Cell Cardiol* 2001 Jan;33(1):141-8.
   - (PubMed: 11133230)
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   - www.hgmd.cf.ac.uk/ac/index.php
9. Maron BJ, McKenna W, Danielson GK, et al., *J Am Coll Cardiol* 2003;42(9):1687-1713.
   - (PubMed: 14585256)

METHOD: Genomic DNA from this specimen was PCR-amplified for analysis the genes in the hypertrophic cardiomyopathy panel: mutation. Bi-directional sequence was obtained and DNA sequence was analyzed and compared to the published gene sequence. This result was confirmed in a new amplicon by repeat sequence analysis. The methods used by GeneDx are expected to be greater than 99% sensitive in detecting mutations identifiable by sequencing.

DISCLAIMER: This assay was developed and its performance determined by GeneDx for the sole purpose of identifying small sequence variants in the gene(s) tested. As with any genetic testing assay, this test does not large chromosomal aberrations, such as large deletions and duplications (larges than 25bp). Normal findings do not rule out the diagnosis of any disorder since some genetic abnormalities may be undetectable with this assay. Clinical implications of some variations may be unknown at the time of this report. This test should be used for clinical purposes only. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary. Pursuant to the requirements of CLIA '88, this laboratory has established and verified the test's accuracy and precision. CLIA ID# 21D0669651. MD License: 953.

Director, Cardiology Genetic Services

Medical Director

GeneDx • 207 Perry Parkway • Gaithersburg, MD 20877 • Tel (301) 519-2100 • Fax (301) 519-2892 • www.genedx.com

Successful Genetics Testing Must Include:

- Obtaining Proper Clinical Information Prior to Testing
- Expert Testing with Minimal Indeterminate Results
- Thorough Reporting based on Academic Sources
- Fully Engaged Genetic Counselors
- Comprehensive Patient & Physician Education

It's More than Just Testing

Clinical Lab Challenges

2009

Two Major Challenges - ~~2001~~

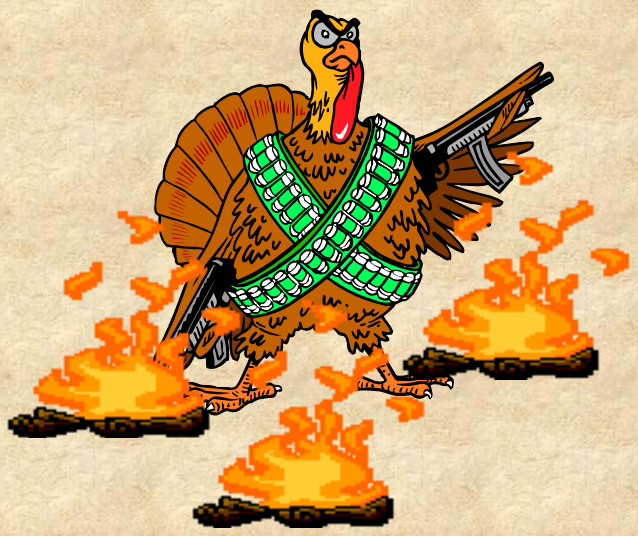
How do you prevent a laboratory from becoming a commodity provider?

How can the Clinical Laboratory deliver greater value?

Critical Assets of the Clinical Laboratory

- **Access**: Laboratories maintain a central position in the healthcare continuum;
- **Laboratories are Ubiquitous** and play an essential role in, diagnosis and monitoring of disease;
- **Data:** Laboratories enable virtually all healthcare analysis;
- **Translate**: Laboratories play a primary role in translating science to patient care.

Call to Arms



2009

Call to Arms

ACCESS

- Let nothing stand between the laboratory and the physician
- Embrace competition
- Fight restrictive arrangements of any kind from any source
- Differentiate your laboratory to the physician user at all costs

Call to Arms

Promote the value of laboratory testing:

- ✓Can't spell prevention without laboratories.
- ✓Utilization is not a four letter word

RESULTS *for* LIFE
LAB TESTING: BETTER HEALTH, IMPROVED OUTCOMES

Results for Life

A Targeted Public Affairs Campaign to Communicate the Value of Laboratory Tests

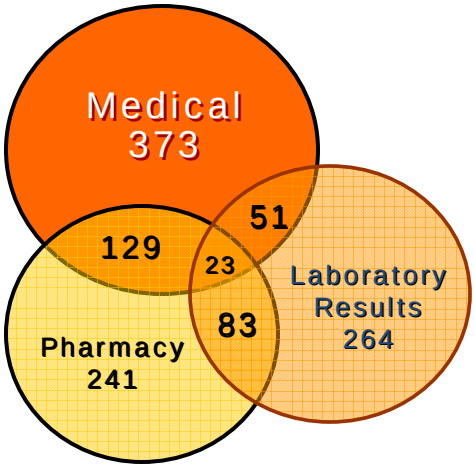
Value of Laboratory Services: Defining A Strategic Vision & Direction

Communication

Call to Arms

Laboratory data remains the essential component of any healthcare analytics

Clinical Relevance



TYPICAL QUERY EXAMPLES

What percent of diabetics had yearly foot exam?

None

What percent of diabetics had eye exams?

4% (25 of 661)

What percent of diabetics had urinary tests for microalbuminuria?

3% (20 of 661)

What percent of diabetics are on ACE Inhibitors?

13% (89 of 661)

Actual Total Diabetic Population - 661

**Information from actual PSIMedica Beta group

2001

Clinical Laboratory eWarehouse

CLeW

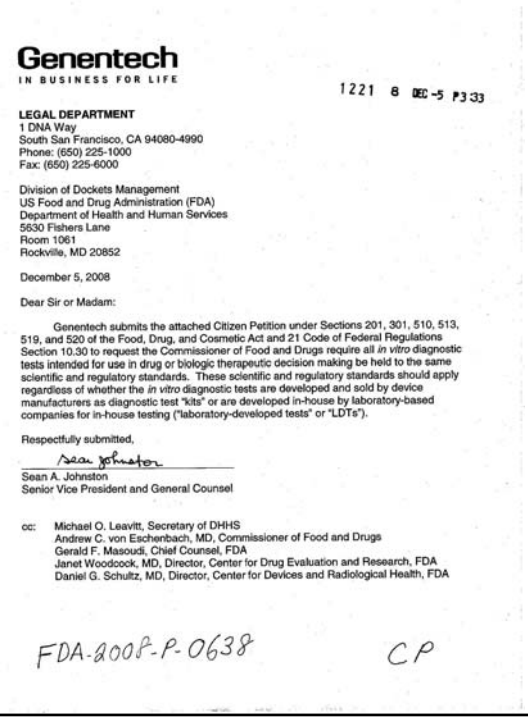
- The value of laboratory results on clinical decision-making has been well documented. On the basis of volume, laboratory results represent by far the largest portion of patient medical records.
- Yet our importance as providers is in constant need of justification. Despite industry consolidation over the years, laboratory results data is spread out over so many separate entities that no single entity can satisfy the healthcare need for access to this data, both on an individual and population basis.
- The need to consolidate the data is so compelling that it is inevitable that a solution will be found somewhere in the near future.
- The clinical laboratory industry needs to take a leadership role in developing and implementing a strategy to meet this vital healthcare initiative.

2009

Call to Arms

- Protect the Translative and Educational Role of clinical Laboratories
  - -Regulation of Laboratory Developed Tests (LDTs)
  - -Exclusive Licensing of Gene Patents

Demonstrate The Value of Laboratory Developed Tests



Genentech
IN BUSINESS FOR LIFE

1221 8 DEC -5 P3:33

LEGAL DEPARTMENT
1 DNA Way
South San Francisco, CA 94080-4990
Phone: (650) 225-1000
Fax: (650) 225-6000

Division of Dockets Management
US Food and Drug Administration (FDA)
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

December 5, 2008

Dear Sir or Madam:

Genentech submits the attached Citizen Petition under Sections 201, 301, 510, 513, 519, and 520 of the Food, Drug, and Cosmetic Act and 21 Code of Federal Regulations Section 10.30 to request the Commissioner of Food and Drugs require all *in vitro* diagnostic tests intended for use in drug or biologic therapeutic decision making be held to the same scientific and regulatory standards. These scientific and regulatory standards should apply regardless of whether the *in vitro* diagnostic tests are developed and sold by device manufacturers as diagnostic test "kits" or are developed in-house by laboratory-based companies for in-house testing ("laboratory-developed tests" or "LDTs").

Respectfully submitted,

Sean Johnston

Sean A. Johnston
Senior Vice President and General Counsel

cc: Michael O. Leavitt, Secretary of DHHS
Andrew C. von Eschenbach, MD, Commissioner of Food and Drugs
Gerald F. Masoudi, Chief Counsel, FDA
Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, FDA
Daniel G. Schultz, MD, Director, Center for Devices and Radiological Health, FDA

FDA-2008-P-0638 CP

2009

Value of Laboratory Developed Tests

-Tests are not designed in Board Rooms

-Respond to rare diseases or relatively rare clinical events

-LDTs Promote Innovation

-Genomic discovery does not lend itself to old ways

■Warfarin (Coumadin) Sensitivity

CYP2C9

CYP2C9*2	(C403T)
CYP2C9*3	(CA1075C)
CYP2C9*4	(T1076C)
CYP2C9*5	(C1080G)
CYP2C9*6	(818)
CYP2C9*11	(A335T)

VKORC 1

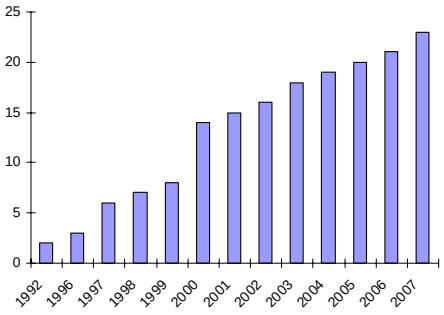
1. -1639	G→A
2. 85	G→T
3. 121	G→T
4. 134	T→C
5. 172	A→G
6. 1331	G→A
7. 3487	T→G
8. 3730	G→A

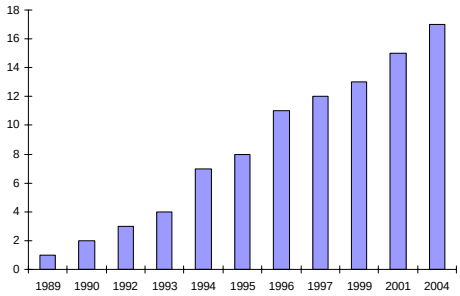
CYP4F2 V433M

VKORC1 (Resistance)

106	G→T

Gene Discovery in Timeline in DCM





Gene Discovery in Timeline in HCM

Statement of Dr. Marc Grodman,
CEO of Bio-Reference Laboratories, Inc.

The House Judiciary Subcommittee on Courts, the Internet and Intellectual Property in Connection with its hearing on "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing"

October 30, 2007

AUTM Recommends Universities Review the 'Nine Points to Consider in Licensing University Technology'

Exclusive licensing of a single gene for a diagnostic may be counterproductive in a multi-gene pathology where only a panel of genes can yield an adequate diagnosis, unless the licensee has access to the other genes of the panel.

SACGHS Public Consultation Draft Report for Public Comment from March 9 to May 15, 2009

Box A: NIH Best Practices for the Licensing of Genomic Inventions

Whenever possible, nonexclusive licensing should be pursued as a best practice. A nonexclusive licensing approach favors and facilitates making broad enabling technologies and research uses of inventions widely available and accessible to the scientific community. When a genomic invention represents a component part or background to a commercial development, nonexclusive freedom-to-operate licensing may provide an appropriate and sufficient complement to existing exclusive intellectual property rights.

[165] HHS. (1999). NIH Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice. *Federal Register* 64(246). December 23. Notices. P. 72090. http://ott.od.nih.gov/pdfs/64FR72090.pdf.

Long QT Syndrome

- Genetic disorder (1:5,000-10,000)
- ECG evidence: QTc interval prolonged
  - >440 ms in males
  - >450 ms in females
- Hallmark arrhythmia: Torsade de pointes VT
- Primary presenting symptom: Syncope
- SCD in children or young adults

Molecular Genetics

Table 1. Molecular Genetics of Long QT Syndrome (LQTS)*

LQTS Type (Year Discovered)	Chromosomal Locus	Mutant Gene (Alternate Name)	Ion Currents Affected by the Mutant Gene
LQT1 (1991)	11p15.5	*KCNQ1* (*KVLQT1*)	Decreased slowly activating delayed rectifier K^+ repolarization current (I_{Ks})
LQT2 (1994)	7q35-36	*HERG*	Decreased rapidly activating delayed rectifier K^+ repolarization current (I_{Kr})
LQT3 (1994)	3p21-24	*SCN5A*	Increased Na^+ current (I_{Na}) due to late reopening of the sodium channel
LQT4 (1995)	4q25-27	Ankyrin B	Possibly increased late Na^+ current (I_{Na})
LQT5 (1997)	21q22.1-22.2	*KCNE1* (minK)	Decreased slowly activating K^+ repolarization current (I_{Ks})
LQT6 (1999)	21q22.1-22.2	*KCNE2* (MiRP1)	Decreased rapidly activating K^+ repolarization current (I_{Kr})
LQT7 (2001)†	17q23	*KCNJ2*	Decreased inwardly rectifying K^+ current ($I_{Kr2.1}$)

*A single mutation (heterozygous state) in any one of the *LQT1* through *LQT7* genes results in an autosomal dominant form of LQTS (Romano-Ward syndrome). The presence of 2 mutations (homozygous state) in either the *LQT1* or *LQT5* gene results in a severe autosomal recessive form of LQTS with associated deafness (Jervell and Lange-Nielsen syndrome).
†Mutations in *LQT7* are responsible for Andersen syndrome, a rare neurologic disorder characterized by periodic paralysis, skeletal developmental abnormalities, and QT prolongation.

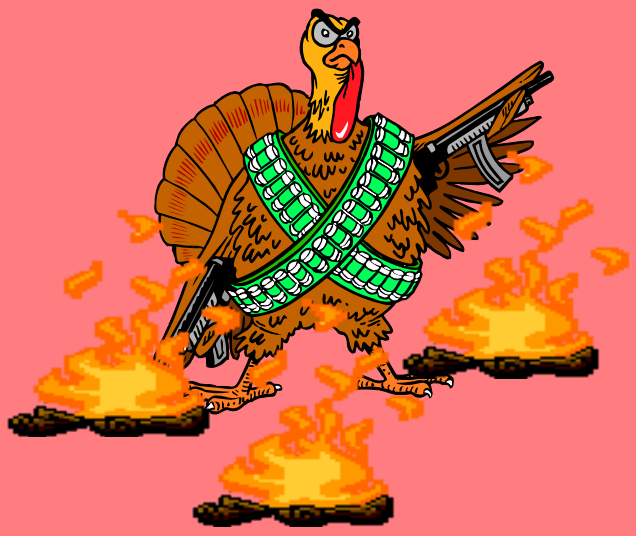
Common Forms of LQTS

Table 1. **Common Forms of the Long-QT Syndrome.***

Variable	Genetic Subtype		
	LQT1	LQT2	LQT3
Disease-associated gene	*KCNQ1*	*KCNH2*	*SCN5A*
In vitro effect	Decreased I_{Ks}	Decreased I_{Kr}	Increased plateau I_{Na}
Setting of arrhythmia†	Emotional or physical stress, swimming, diving	Emotional or physical stress, sudden loud noise	Rest, sleep
Typical resting ECG‡	Broad T wave	Low-amplitude T wave with notching	Long isoelectric ST segment
ECG at onset of arrhythmia§	No pause	Pause	Not established
QT change with exercise	Failure to shorten	Normal	Supranormal
QT shortening with mexiletine¶	No	No	Yes
Clinical response to beta-blockers‖	Yes	Less than LQT1 response	Uncertain

* ECG denotes electrocardiogram, I_{Kr} the rapid component of the delayed rectifier current, I_{Ks} the slow component of the cardiac delayed rectifier current, and I_{Na} the cardiac sodium current.
† Data are from Schwartz et al.[4]
‡ These are typical patterns, but exceptions and variants are well recognized. Data are from Moss et al.[5]
§ Data are from Tan et al.[6]
¶ Data are from Schwartz et al.[7]
‖ Data are from Priori et al.[8]

Call to Arms



2009 - ???

BioReference LABORATORIES

Then ….

Now ….

Next ….

2009 Executive War College

April 28, 2009

Presented by: Marc D. Grodman, MD, CEO

2009