



Clinical Cytogenomics Laboratory

Leading diagnostics for better medicine

Beaumont
Laboratory



Beaumont Laboratory's Clinical Cytogenomics Lab

Genome decoding is essential

Knowledge of variations in genome sequence and structure is critical to understand medical conditions ranging from cancer to hereditary genetic disorders. Changes ranging from genomic duplications and deletions to single-nucleotide changes all have considerable and complex effects on individuals and their treatments. Genome exploration is an essential component of a testing protocol for individuals with congenital malformations, intellectual disability, multiple spontaneous miscarriages or infertility, also for individuals with hematologic neoplasms and solid tumors. Cytogenetic and genomic analysis can be performed on a variety of tissues including fresh blood, bone marrow, prenatal specimens, solid tumors and other tissues.

PATIENT-CENTERED, BOARD-CERTIFIED PATHOLOGISTS

To provide you with a broad scope of consultative and diagnostic services, Beaumont Laboratory has assembled many highly regarded pathologists trained at premier institutions throughout the country. Our team includes individuals board certified in hematopathology, cytopathology, neuropathology, pediatric pathology, dermatopathology, surgical pathology, clinical cytogenetics, clinical molecular genetics and molecular genetic pathology.

Our medical staff members are easily accessible, collaborative and patient-centered. They are highly specialized and understand the critical components of patient testing, from the physician's needs to the dynamic environment of hospital-based testing. The laboratory medical directors are available for pre- and post-test consultations, to speak directly with physicians and other health care professionals about:

- appropriate cytogenetic/molecular test utilization
- interpretation and prognostic significance of results
- recommendations for further testing and/or genetic counseling of the patient or family members

DIAGNOSTIC INSIGHTS FROM LEADING-EDGE TECHNOLOGY

The clinical Cytogenomics Laboratory, led by a board-certified cytogeneticist/clinical molecular geneticist provides conventional, molecular cytogenetic chromosome analysis, and chromosome microarray analysis using state of the art technologies. Testing turnaround time is two to ten days depending on the assay. The testing offered includes:

- Conventional chromosome studies (karyotyping) and genome-wide single nucleotide polymorphism (SNP) molecular karyotyping
 - prenatal
 - constitutional
 - oncologic
- Molecular cytogenetic (fluorescence in situ hybridization [FISH]) analysis:
 - prenatal aneuploidy detection
 - microdeletion/microduplication syndromes
 - hematolymphoid malignancies and solid tumors



Mark Micale, Ph.D., FACMG

Director, Clinical Cytogenomics Laboratory

*Associate Professor, Department of Pathology and Laboratory Medicine
Medical Genetics Curriculum Director, Oakland University William
Beaumont School of Medicine*

Board certification

- Clinical Cytogenetics
- Clinical Molecular Genetics
- American Board of Medical Genetics

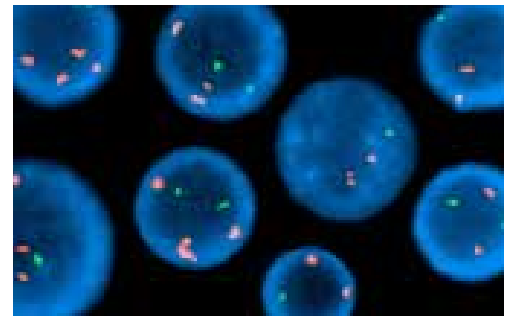
Special interests

- Cancer Cytogenetics
- Array-based Cytogenomic Analysis

ONCOLOGIC CYTOGENETIC ANALYSIS

- **Conventional chromosome analysis** identifies structural or numerical chromosome abnormalities characteristic of a variety of malignancies. Identification of these lesions provides important diagnostic and prognostic information.
- **SNP-array molecular karyotyping** can identify clinically significant genomic imbalance along with copy number neutral loss of heterozygosity (uniparental disomy). Identification of these lesions can provide important diagnostic and prognostic information.
- **Molecular cytogenetic (FISH) analysis** is performed on all oncology tissue types, including bone marrow, peripheral blood, lymph node, tumor biopsy specimens, and paraffin tissue to identify characteristic chromosome abnormalities important for confirmation of diagnosis, disease classification, staging, prognosis, determining appropriate therapy and identifying remission or relapse.

Beaumont Cytogenomics Laboratory is an approved Children's Oncology Group (COG) lab capable of performing all cytogenetic testing for children on COG protocols.



Conventional chromosome analysis is performed on all oncologic tissues including

- bone marrow
- peripheral blood
- solid tumors
- lymph nodes
- other tissues

Applications of SNP array analysis in oncology

- chronic lymphocytic leukemia
- myelodysplastic syndrome/ myeloproliferative neoplasm
- plasma cell myeloma
- acute lymphoblastic leukemia
- acute myeloid leukemia
- renal cell carcinoma
- neuroblastoma

Applications of FISH analysis in hematolymphoid malignancies

- Disease-specific FISH panels and single FISH assays for
- acute B- and T- lymphoblastic leukemia
 - acute myeloid leukemia
 - chronic lymphocytic leukemia
 - chronic myelogenous leukemia
 - myelodysplastic syndrome/ myeloproliferative neoplasm
 - plasma cell myeloma
 - non-Hodgkin lymphoma
 - myeloid and lymphoid neoplasms associated with PDGFRA rearrangement

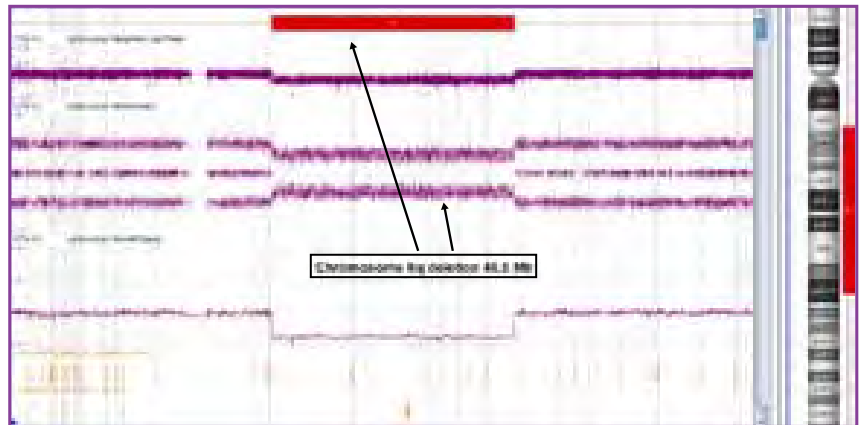
Applications of FISH analysis in solid tumors

- alveolar rhabdomyosarcoma
- desmoplastic small round cell tumor
- Ewing's sarcoma
- synovial sarcoma
- myxoid liposarcoma
- synovial sarcoma
- ALK gene rearrangement in non-small cell lung carcinoma

BEAUMONT AFFYMETRIX CYTOSCAN® HD SINGLE NUCLEOTIDE POLYMORPHISM (SNP) ARRAY

This test provides the broadest coverage and highest performance for detecting both copy number altering and copy number neutral aberrations. CytoScan HD Array has greater than 99 percent sensitivity and can reliably detect 25-50 kb copy number changes across the genome. With 2.67 million copy number markers (akin to performing 2.7 million simultaneous FISH experiments, including 750000 SNP's), the Beaumont CytoScan Array offers high-density resolution of the entire genome, for relevant aberration detection and reporting. The array includes 100% Sanger Cancer Gene coverage, 100% ICCG Constitutional Gene Coverage, and 12,000 OMIM® genes.

SNP array results obtained from a bone marrow specimen reveals a 48.5 Mb chromosome 6q deletion in a patient with chronic lymphocytic leukemia. The deleted segment lies between bands 6q13 and 6q22.31. FISH to evaluate the MYB gene, which lies just distal to the deleted segment and is used as a FISH marker for del(6q) was negative; however, SNP array identified a large deletion proximal to the MYB gene. Such deletions in CLL predict an intermediate risk.



SNP array results obtained from a peripheral blood specimen of a four-year-old male referred for seizures, profound sensorineural hearing loss, moderate cognitive impairment, and speech delay demonstrated a 10kb deletion resulting in removal of exons 15-18 of the SCN1A gene on chromosome 2q24.3. The SCN1A gene, which codes for the alpha-1 subunit of neuronal voltage-gated sodium channels, is one of the most clinically relevant of all known epilepsy genes. Mutations in this gene are associated with a variety of seizure disorders. The diagnosis of an SCN1A mutation aids in the selection of antiepileptic drugs, as some drugs such as sodium-channel blocking agents may exacerbate symptoms. This is a great example of personalized medicine.



CONSTITUTIONAL CYTOGENOMIC ANALYSIS

- conventional cytogenetic analysis (karyotyping) of peripheral blood and skin
- SNP-array molecular karyotyping
- FISH analysis for microdeletion/microduplication syndromes

Pediatric and adult genetic assessment for:

- developmental delay/intellectual disability
- dysmorphic features
- multiple congenital anomalies
- autism/autism spectrum disorder
- seizures
- behavior problems
- microdeletion/microduplication syndromes not amenable to FISH testing

Microdeletion/microduplication syndromes

- Wolf-Hirschhorn
- Williams
- Cri du chat
- Prader-Willi/Angelman
- Miller-Dieker
- Smith-Magenis
- 22q11.2 [DiGeorge/velocardiofacial]

PRENATAL CYTOGENOMIC ANALYSIS

- conventional cytogenetic analysis (karyotyping) of amniotic fluid, chorionic villus sampling, products of conception, and fetal blood
- prenatal aneuploidy detection of amniotic fluid/ CVS specimens by FISH with next business day turnaround time
- product of conception aneuploidy detection by paraffin FISH analysis
- SNP array molecular karyotyping of amniotic fluid/ CVS specimens to identify a cytogenetic abnormality in a fetus with multiple anomalies identified by ultrasound and a normal karyotype

Chromosome microarray analysis is now recommended as a front-line test in any pregnancy with one or more fetal ultrasound anomalies [ACOG and The Society for Maternal-Fetal Medicine. The use of Chromosomal microarray analysis in prenatal diagnosis (2013). Committee opinion No 581]

Yield of chromosome microarray analysis in prenatal cases with ultrasound anomalies and a normal karyotype

Study	Multiple Anomalies	CNS Malformation	Cardiovascular	Hydrops/ Cystic Hygroma/NT	Skeletal	Diaphragmatic Hernia/ Gastrointestinal	Craniofacial
Vestergaard et al (2013), Acta Obstet Gynecol Scand 90 cases	1/22 (4.5%)	2/17 (11.8%)	2/9 (22%)	2/6 (33%)	3/19 (15.7%)		
Lee et al (2012), BJOG 3,171 patients	6/39 (15.4%)	4/22 (18.2%)	7/50 (14%)	1/17 (6.7%)	2/23 (8.7%)	1/7 (14.3%)	
Shaffer et al (2012), Prenat Diagn 2,858 patients	58/579 (10%)	23/326 (7.1%)	6/193 (3.1%)	10/232 (4.3%)	15/165 (9.1%)	1/9 (11.1%)	3/70 (4.3%)

SAMPLE COPY OF REPORT/RESULTS

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HEALTH
SYSTEM

Beaumont Laboratory

Clinical Cytogenomics Laboratory
Whole Genome SNP Microarray Consultation Report

CTG-13-138

Patient: TEST, PATIENT

DOB: 01/01/1999 (14 Y) Gender: F

MRN: 6000020

HAR: 6000052003

Patient Phone #:

Physician:

NPI: 1497734487

Location: BED MANAGEMENT RO

Loc ID: RIT

cc:

Collecter: 5/3/2013 2:03 PM

Received: 5/3/2013 2:54 PM

Lab Order#:

Clinical History: Chronic lymphocytic leukemia

CTG-13-138

Specimen Type: Bone Marrow

Chronic Lymphocytic Leukemia Cytogenomic Profile

SNP Oligonucleotide Microarray Karyotype: arr 13q12.3q21.1(30852239-56193940)x1

Interpretation: SNP array karyotyping revealed a 25.5 Mb heterozygous deletion of chromosome 13q12.3-q21.1 that involves the RB1 gene. These results indicate a higher risk of an accelerated clinical course in this patient.



Summary of CLL-Associated Chromosome Abnormalities: The most common recurrent chromosomal abnormalities in CLL include deletion 13q14, trisomy 12, and deletions of chromosomes 6q, 11q (including the ATM gene), and 17p (including the p53 gene). Prognostic categories have been established, whereby del(11q) and del(17p) chromosomes are associated with faster disease progression and inferior survival, while the del(13q) chromosome as the sole abnormality has been associated with a favorable outcome; however, microarray analysis has delineated two distinct chromosome 13q14 deletions with specific clinical outcomes. The smaller type I deletion is associated with a better outcome, whereas the type II deletion (generally larger than 2Mb) includes loss of the RB gene and is associated with an accelerated clinical course. Trisomy 12 predicts an intermediate prognosis while a del(6q) chromosome demonstrates a higher white blood cell count and more extensive lymphadenopathy, but is of uncertain prognostic significance. Overall, CLL cases with greater numbers of copy number changes (elevated genomic complexity) identifies a CLL subset that will demonstrate a more aggressive clinical course and poorer survival. In addition to genomic imbalances, copy-number neutral loss of heterozygosity (CN-LOH) or uniparental disomy which can be identified by SNP array has also demonstrated clinical significance, including CN-LOH on chromosome 13q associated with biallelic del(13)(q14) deletions and CN-LOH on chromosome 17p associated with homozygous TP53 gene mutations.

References:

- 1) Edelmann J et al (2012): High-resolution genomic profiling of chronic lymphocytic leukemia reveals new recurrent genomic alterations. *Blood* 120: 4783-4794.
- 2) Malek SN (2012): The biology and clinical importance of acquired genomic copy number aberrations and recurrent gene mutations in chronic lymphocytic leukemia. *Oncogene*: 1-13.
- 3) Zenz et al (2011): Importance of genetics in chronic lymphocytic leukemia. *Blood Reviews* 25: 131-137.

For questions/concerns please contact: 800-551-0488

Beaumont, Royal Oak
3601 W 13 Mile Road, Royal Oak, MI 48073

Beaumont, Troy
44201 Douglas Road, Troy, MI 48068

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480 Cadillac Road, Grosse Pointe, MI 48230

TEST, PATIENT

CTG-13-138

6000052003

www.beaumont.edu/088

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ORDERING TESTS AND RECEIVING RESULTS

Paper requisitions or electronic ordering

- Cytogenomic-based requisitions
- Online ordering: Beaumont Labworks
 - website for ordering and receiving results
 - 24-hour access to results

Manual orders

Manual orders are available for clients who are not configured to submit online orders, or clients who normally use paper forms. Please call customer service at 800-551-0488 for a complete list of requisitions.

Beaumont Labworks online ordering

Beaumont Labworks is an online application to connect to the Beaumont Laboratory. Labworks provides an efficient ordering and reporting system. If you are not currently set up with an account, please call Customer Services at 800-551-0488.

BONE MARROW BIOPSY

Bone marrow samples may be conveniently acquired two ways:

1. Hospitals, physicians, labs and medical centers may send samples to the laboratory using convenient bone marrow biopsy kits. Please contact Beaumont Laboratory customer service for additional information: 800-551-0488.
2. At any of our three hospital campuses, our specialized staff use procedures that are quick, less painful for patients and are 98 percent successful in capturing core samples on the first attempt. Our procedures also ensure patients less pain the day after the procedure.

Patients can schedule a procedure by either calling for an appointment or requesting an appointment online:

www.beaumont.edu/request-an-appointment

Patient brochures explaining the procedure are also available, please ask your sales representative for more information.



CUSTOMER SERVICE

Help is available 24/7 for specimen collection, test ordering (online or manual) and shipping information. Our Customer Service team provides personalized and timely service 24 hours a day, seven days a week.

For additional information on test selection, recommendations for further testing, result interpretation and requests related to consultation, please call Customer Service at 800-551-0488 to reach one of our team members.

Our commitment to you is that we will provide timely, accurate, and complete diagnostic information for the optimal care of your patients. The Beaumont Laboratory team will be available to you at all times to answer questions or concerns, or to address matters of urgency.

Our goal is to:

- provide answers to your questions on the first call
- provide critical results within 50 minutes of completion
- answer client calls within 20 seconds, with average time of 15 seconds

CLINICAL CYTOGENOMIC LABORATORY CONTACT INFORMATION

For medical issues concerning cytogenetic/cytogenomic tests contact:

Mark Micale, Ph.D.

248-898-9063

mmicale@beaumont.edu

For specimen requirements, specimens received, tests pending, shipping information, etc. contact:

Customer Service

800-551-0488

For establishing a Beaumont Laboratory account contact:

Customer Service

800-551-0488

BLCustomerService@Beaumont.edu





EDUCATION IS IN OUR DNA

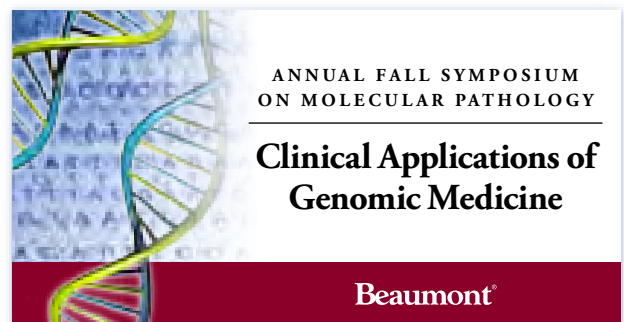
Beaumont Laboratory's strong commitment to education is the foundation upon which our outstanding patient care is built. Beaumont is one of the busiest hospital systems in the country, where students gain a wealth of experience through our interesting specimen caseload. We offer accredited educational programs for pathology and laboratory medicine professionals.

The Beaumont laboratory staff are on the faculty for:

- Beaumont Pathology Residency Program
- Oakland University William Beaumont School of Medicine
- Beaumont School of Medical Technology
- Beaumont Schools of Histotechnology (histotechnologists and histologic technicians)
- Annual DNA Symposium since 1991

Please join us for the annual Beaumont Laboratory DNA Symposium. This program has been designed for physicians, residents, scientists, technologists and other bio-scientific staff who practice in the fields of clinical pathology, hematology/hemostasis, infectious diseases, microbiology, molecular pathology, oncology and toxicology.

For help with registration, contact
Rita Najjar at 248-551-6269
rnajjar@beaumont.edu.



CONTINUING EDUCATION CREDIT

Accreditation: William Beaumont Hospital is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit: William Beaumont Hospital designates this live activity for a maximum of 10.75 *AMA PRA Category 1 credits*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Certificates of Credit: Attendees who sign in each day of the conference, complete an evaluation form, and submit a request for certificate of credit, will receive a certificate of credit by U.S. mail within one month of this activity.

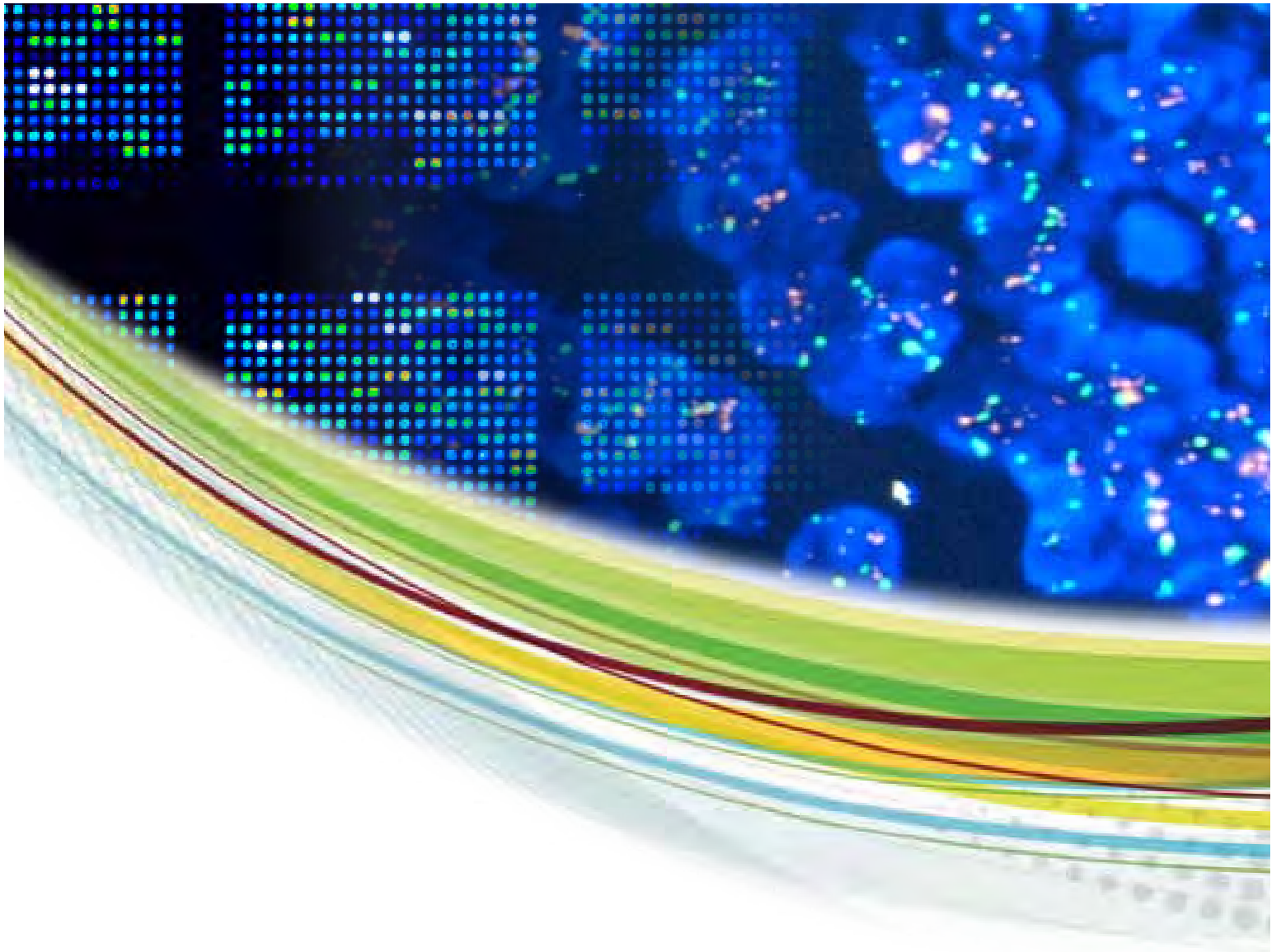
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your patients count on you.**

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