“Quantifying Your Gut: a Personal Journey”

Invited Talk

Osteopathic and Cranial Academy Forum

San Diego, CA

June 13, 2019

Dr. Larry Smarr

Director, California Institute for Telecommunications and Information Technology

Harry E. Gruber Professor,

Dept. of Computer Science and Engineering

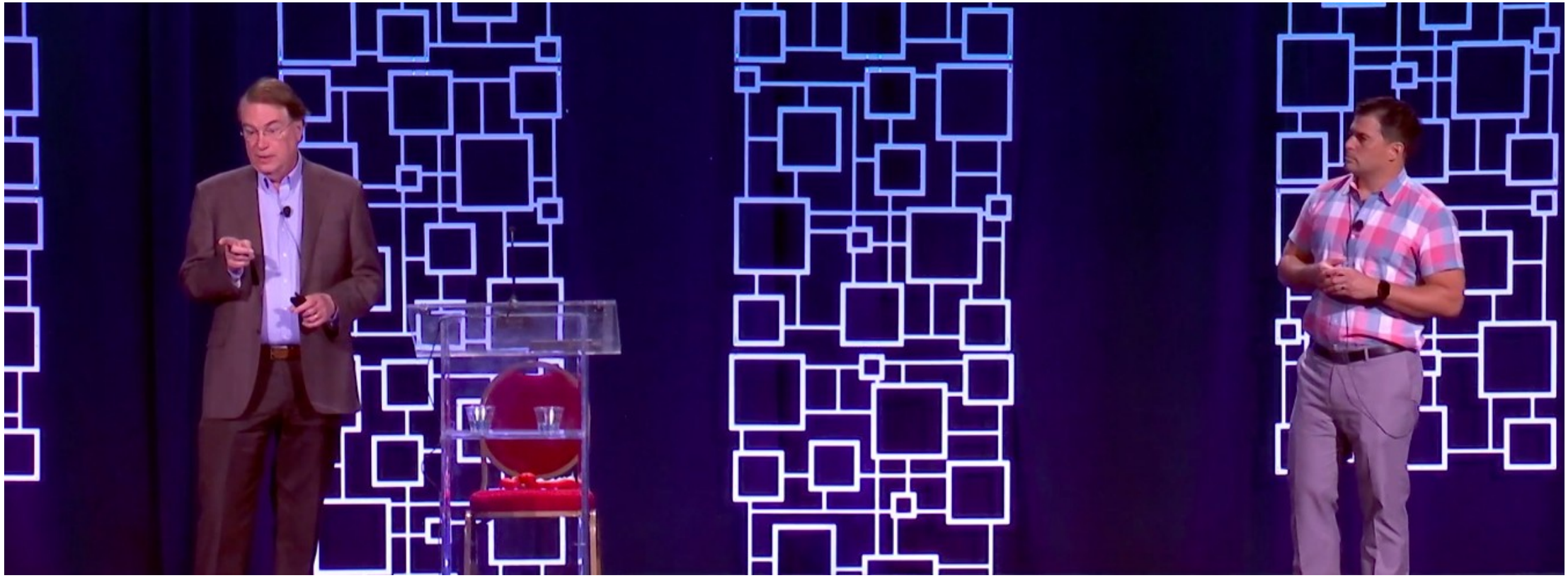
Jacobs School of Engineering, UCSD

http://lsmarr.calit2.net

Larry Smarr
Disclosure Slide

- **Private Sector SAB Member**
  - MD Revolution
  - Mint Health
  - AV Lab, Inc.
  - Torrent Ventures
  - Hu-manity.co
- **Shares in Public Traded Stock:**
  - Tocagen
- **Consultant**
  - Fellow, Price Waterhouse Coopers
- **Nonprofit Boards**
  - Corporation for Education Network Initiatives in California (CENIC)
- **Research Funding**
  - University of California
  - National Science Foundation
  - Helmsley Charitable Trust

Transformative Communication Between Doctor and Patient



Using Advanced Technology to Better Diagnose Somatic Dysfunction

Joint Presentation to the American Academy of Osteopathy
2017 Convocation

https://youtu.be/RsUmB8VpqGE

Dr. Kurisu Physical Exam of Larry Smarr August 2014
Part One: The Spine

Cranial: Vagus Compression R

Lumbar: L3 RR, L4 L5 E, RL

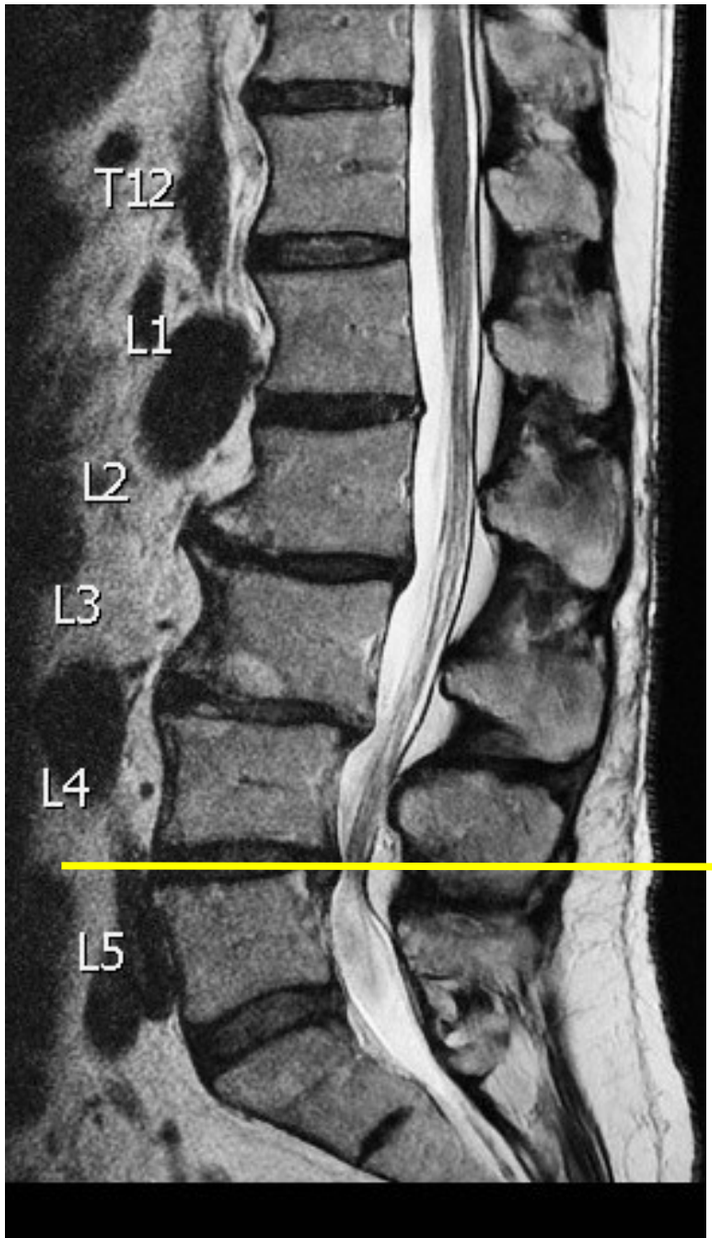
Sacrum: R/L, R SI Joint Dsfxn

LE: Bil Ankle Stiffness

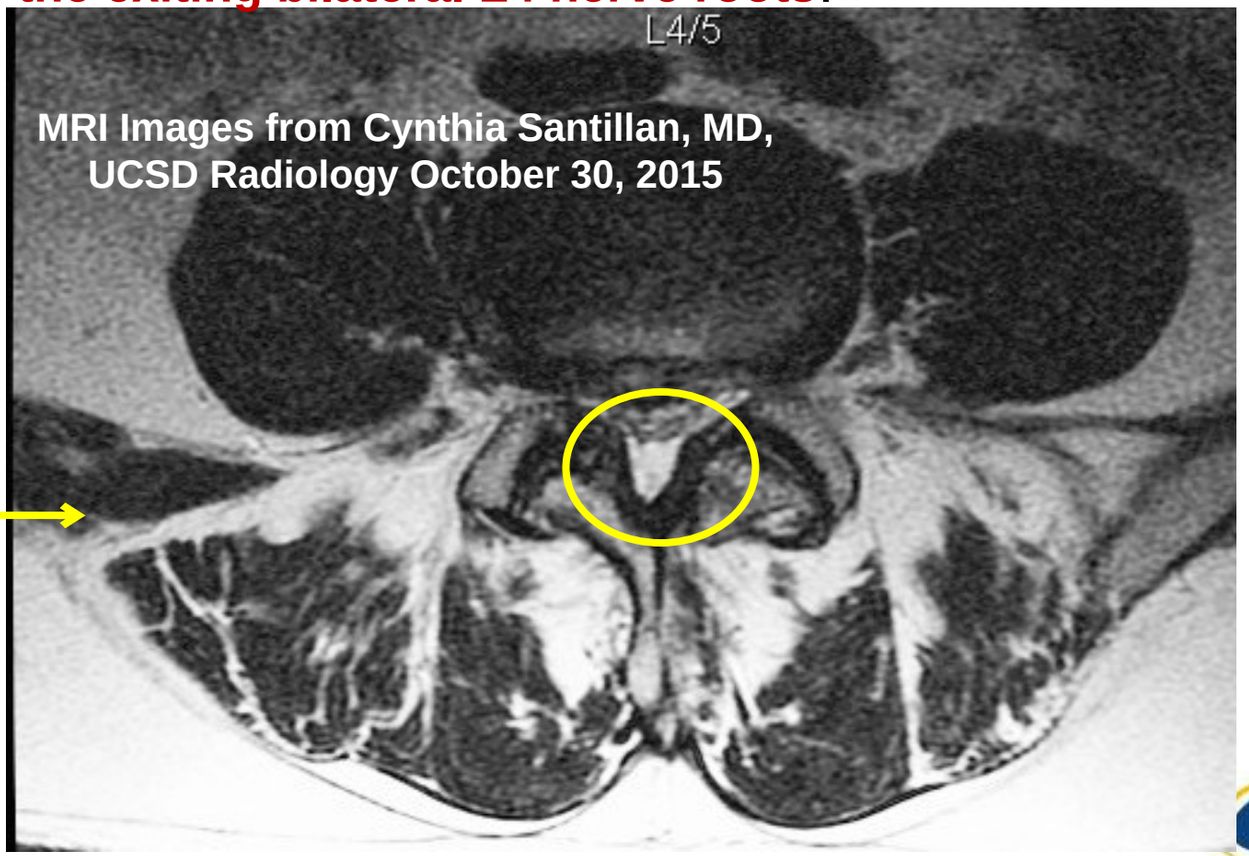
GI: Fascial Restriction Spleen, Colon

Patient Complained of Sciatica and Exhibited Right Foot Drop

MRI Shows Central Canal Stenosis



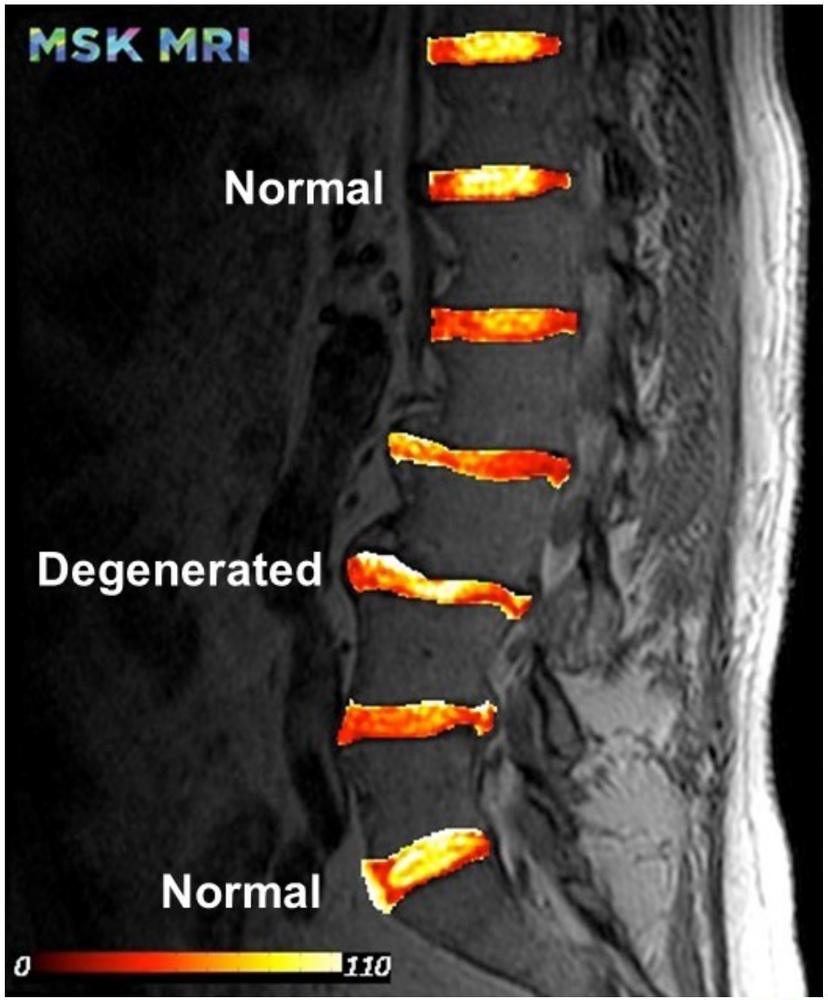
L4-L5: Circumferential disc bulge extends slightly inferiorly in an area of deficiency of the posterior aspect of the L5 superior endplate. Combined with moderate facet arthropathy and ligamentum flavum redundancy, **there is severe central canal stenosis with near complete effacement of Cerebrospinal Fluid (CSF) and mass effect on the cauda equina. Severe bilateral foraminal stenosis, with compression of the exiting bilateral L4 nerve roots**.



Advanced MRI:
Locating Disc Degeneration and Spinal Stenosis



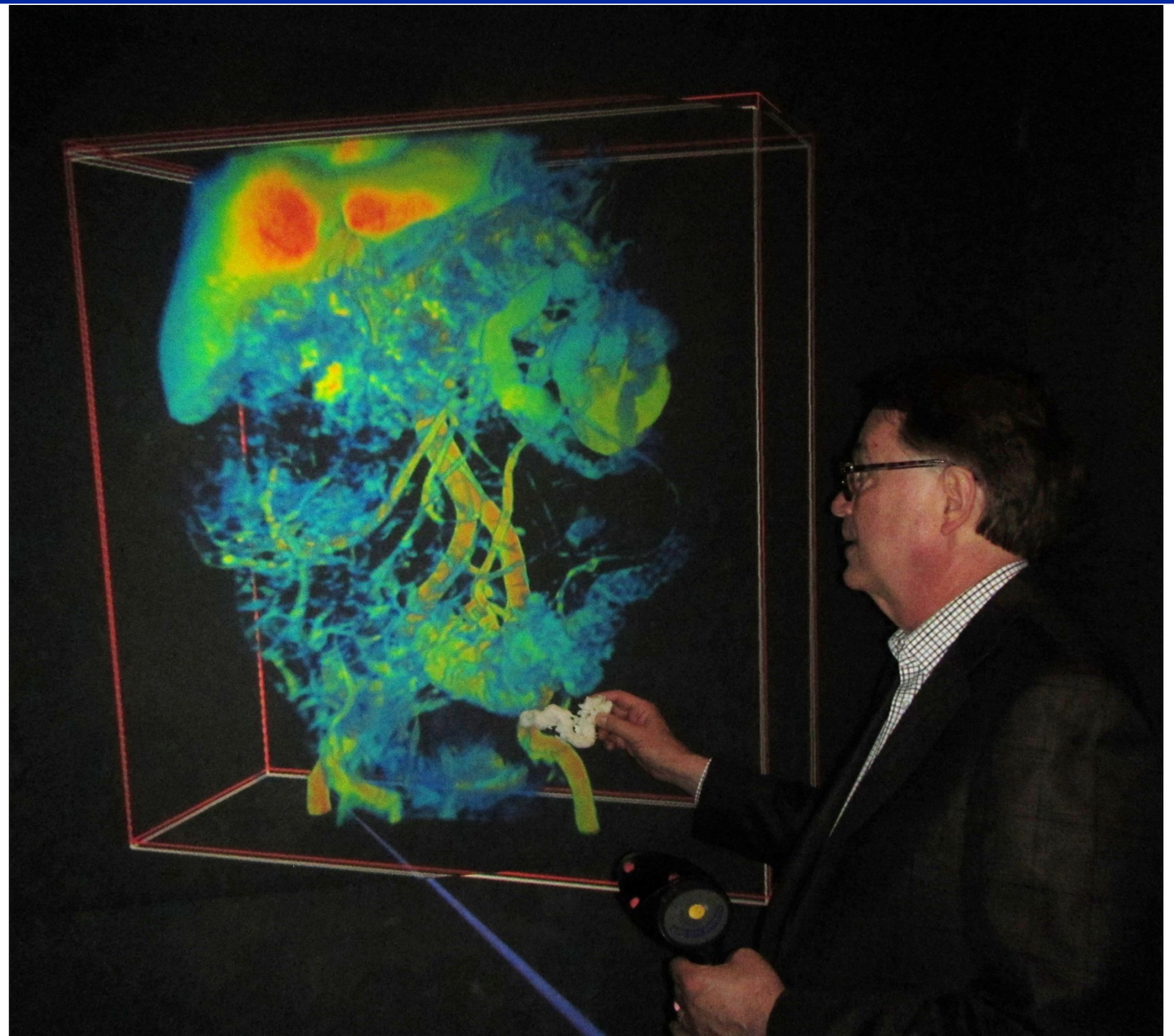




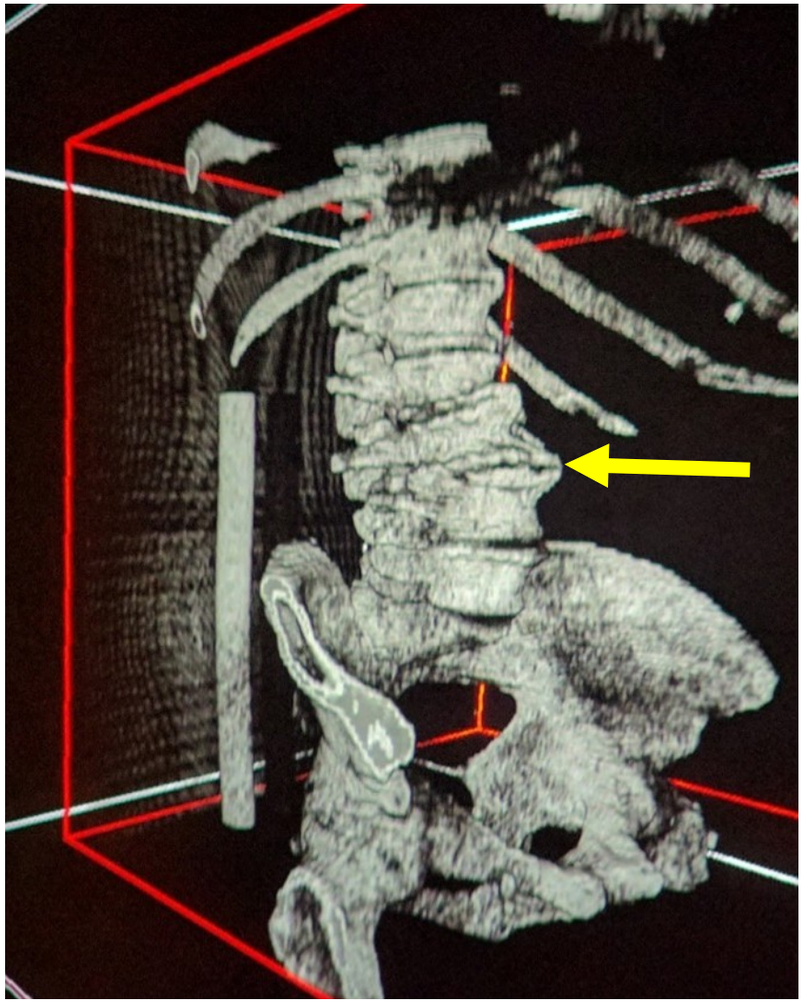
Images courtesy of Christine Chung MD, UCSD MSK Imaging Research Lab (www.MSKMRI.com)

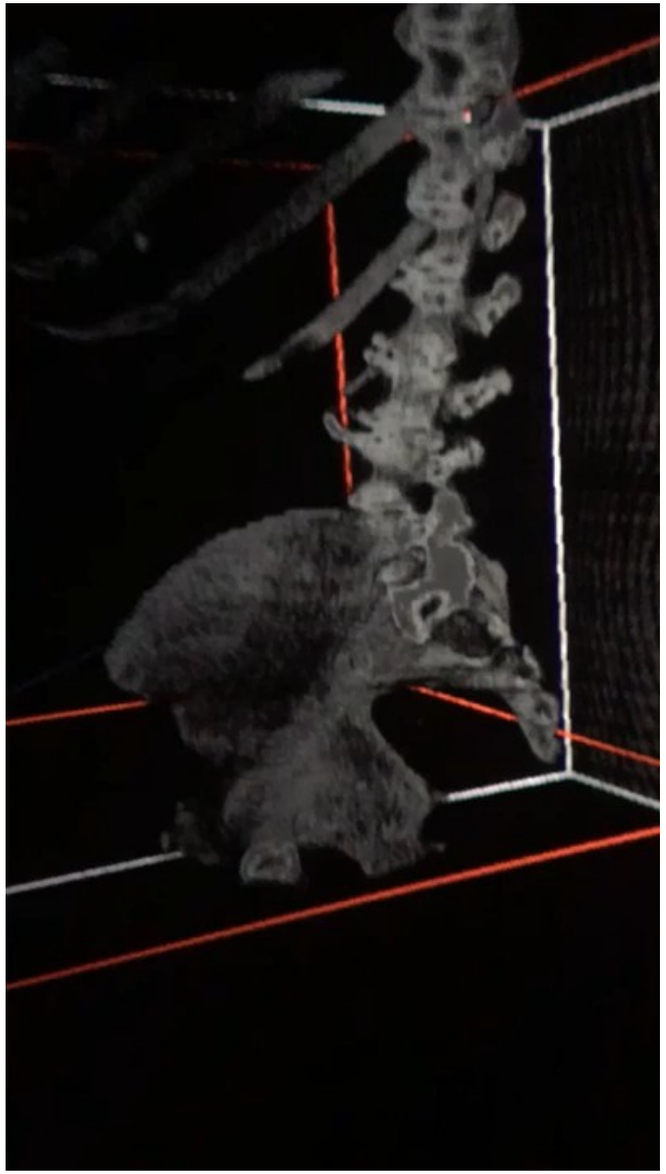
We Have Developed Software at Calit2 To Convert MRI Slices to 3D “Transparent Patient”

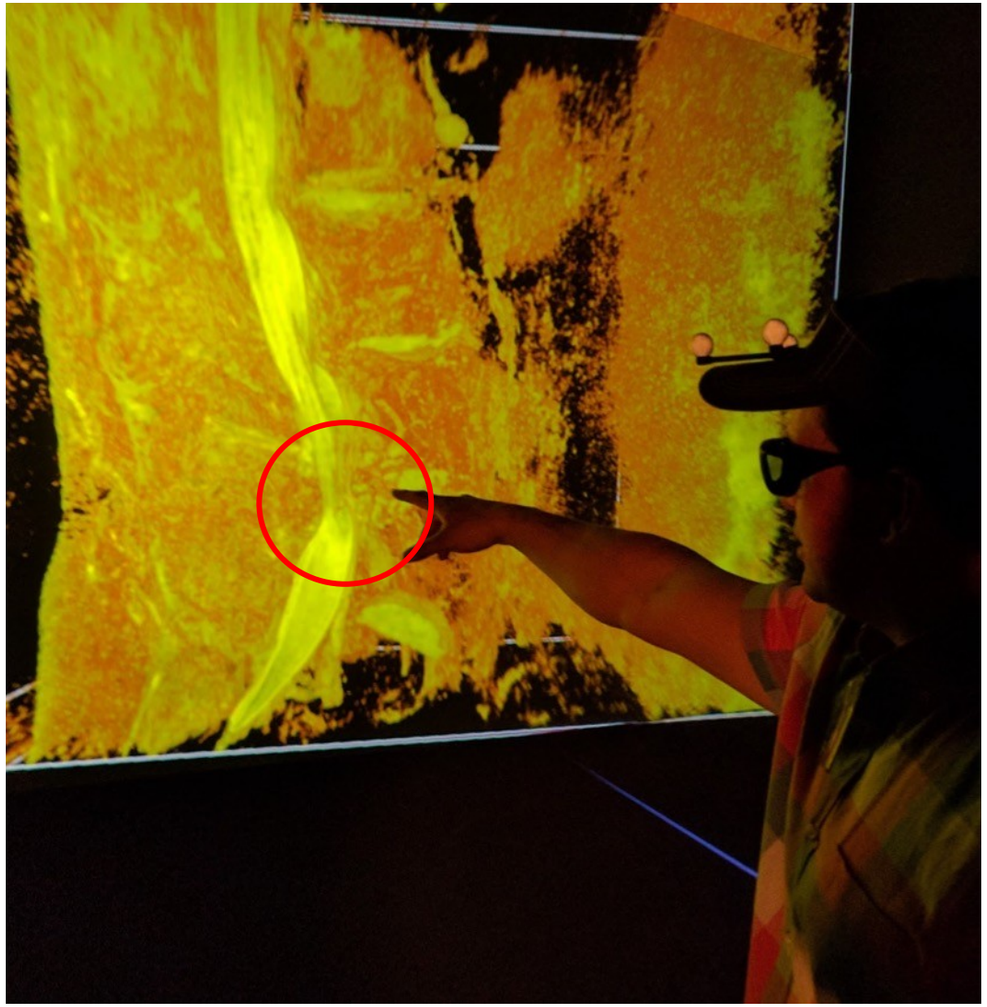
3D Volumetric Visualization Created by Calit2’s Jurgen Schulze from January 2012 MRI



Dr. Kurisu Validating His Osteopathic Findings on My Spine Using 3D MRI Virtual Reality







Visualizations from MRI by Jurgen Schulze, Calit2, UCSD

Dr. Kurisu's OMT Immediately Cured My Sciatica and Greatly Improved My Foot Drop

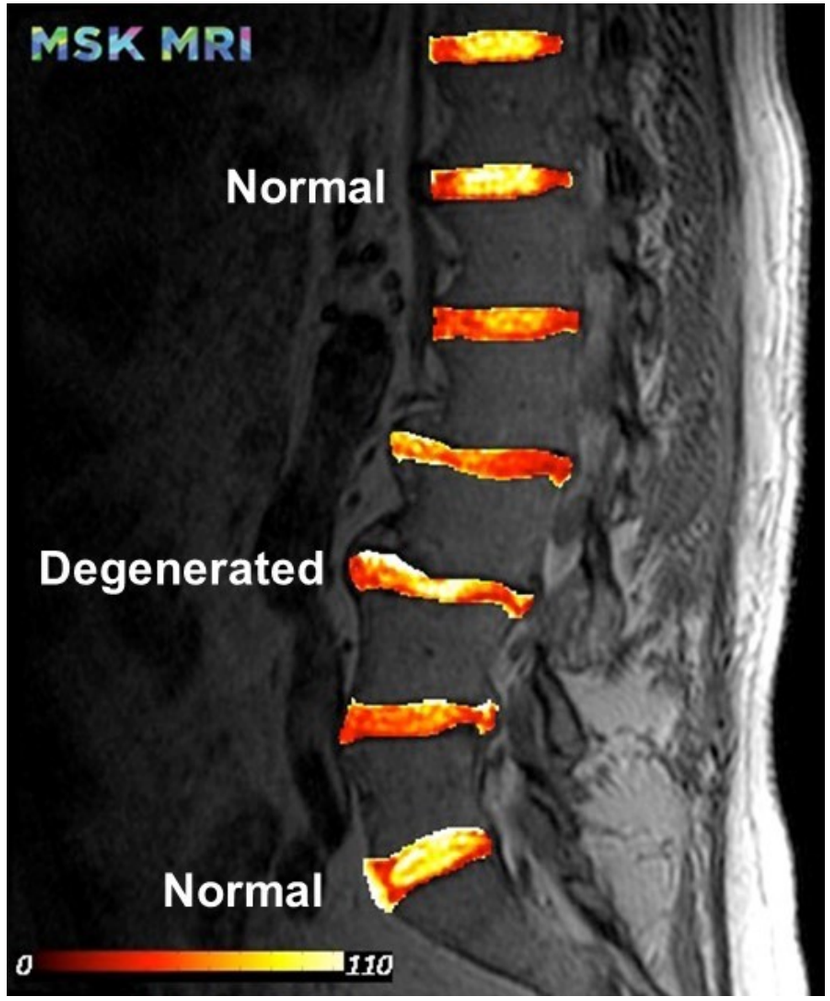


UCTV Video *Future Doctor*
www.youtube.com/watch?v=q4WlN8se8Ac

Dr. Kurisu Physical Exam of Larry Smarr August 2014
Part Two: The Abdomen

Cranial: Vagus compression bilaterally
Lumbar: L5 compressed on R
Sacrum: stabilized
LE: Bil ankle stiffness R>L
GI: Fascial Restriction Spleen, moderately distended descending colon, warmth, mass effect felt sigmoid junction with increasing density

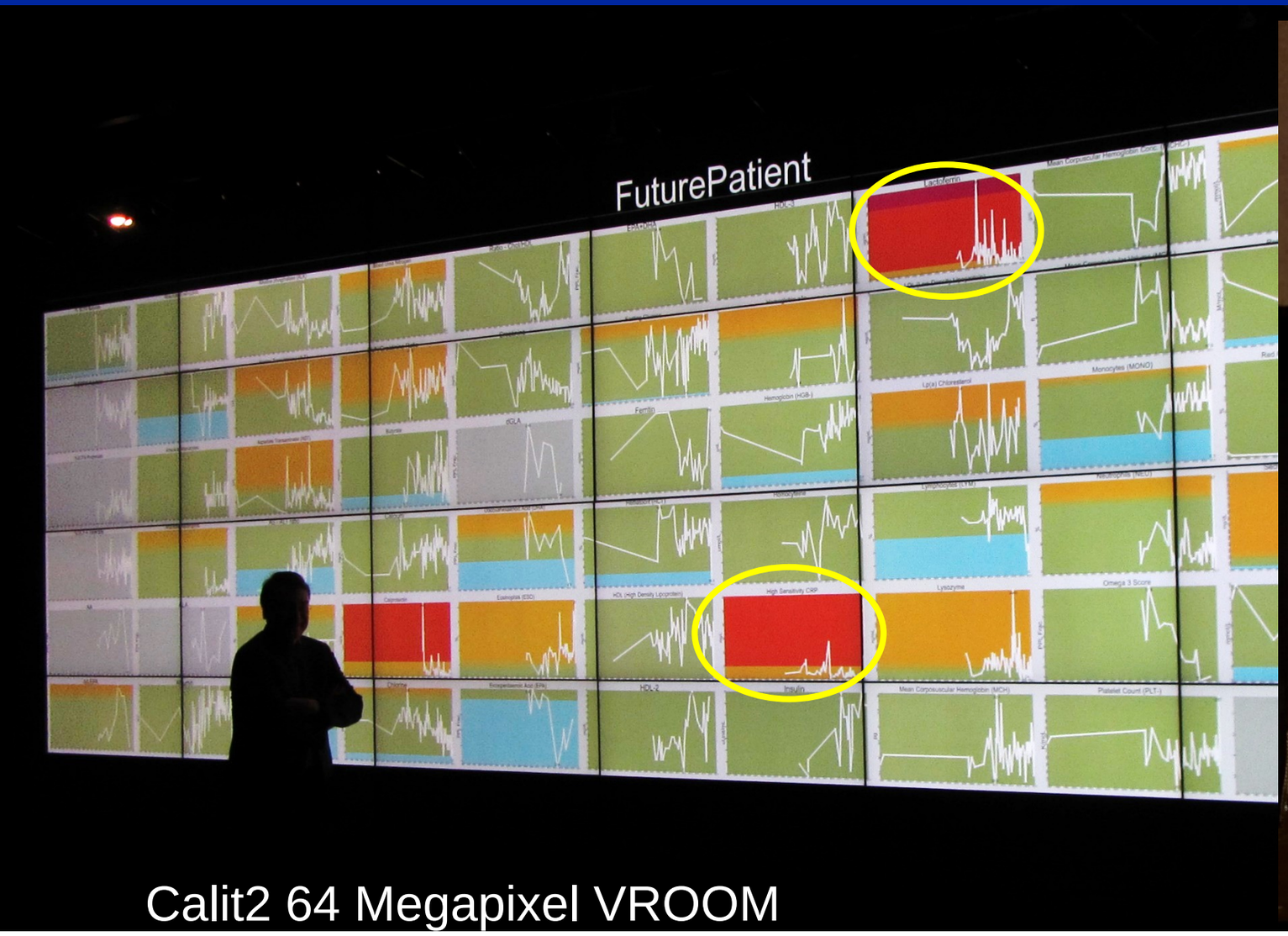
Osteopaths Believe That the Spine and the Abdomen Have a Viscero-Somatic Connection



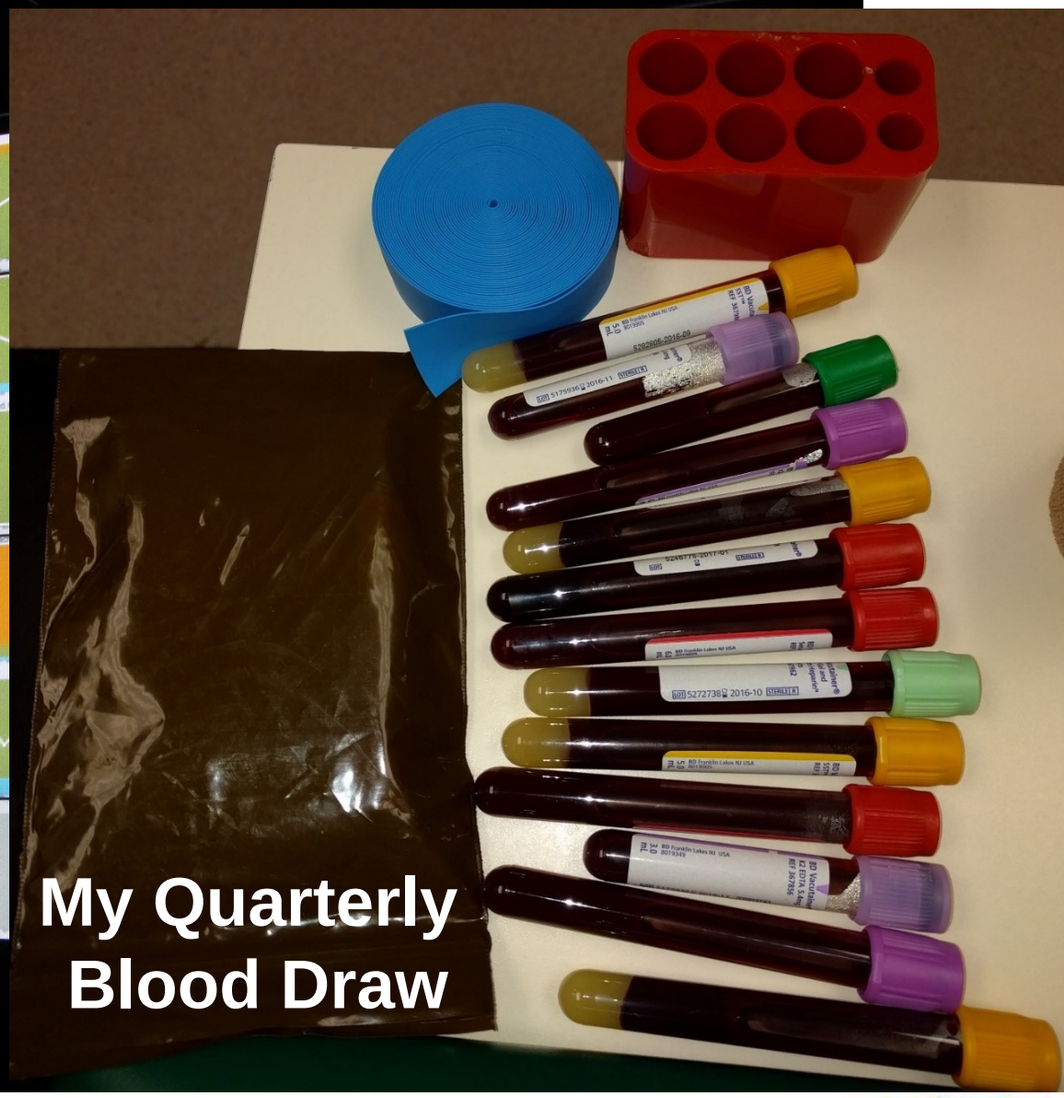
Could My Spine and Gut Issues Be Caused by Chronic Inflammation?



I Have Been Exploring for a Decade the Application of Data Science to Combining Biomarker Time Series with Digital Imaging in a Clinical Setting

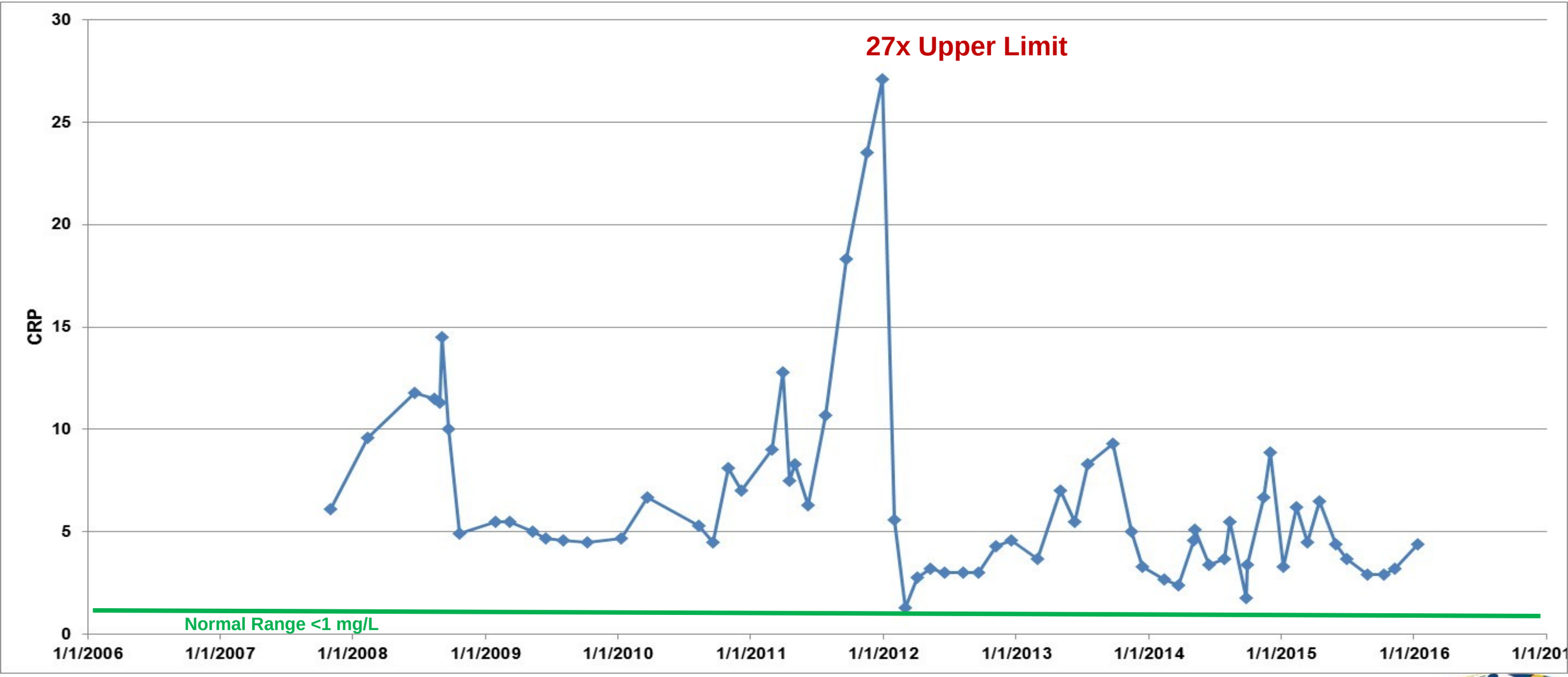


Calit2 64 Megapixel VROOM



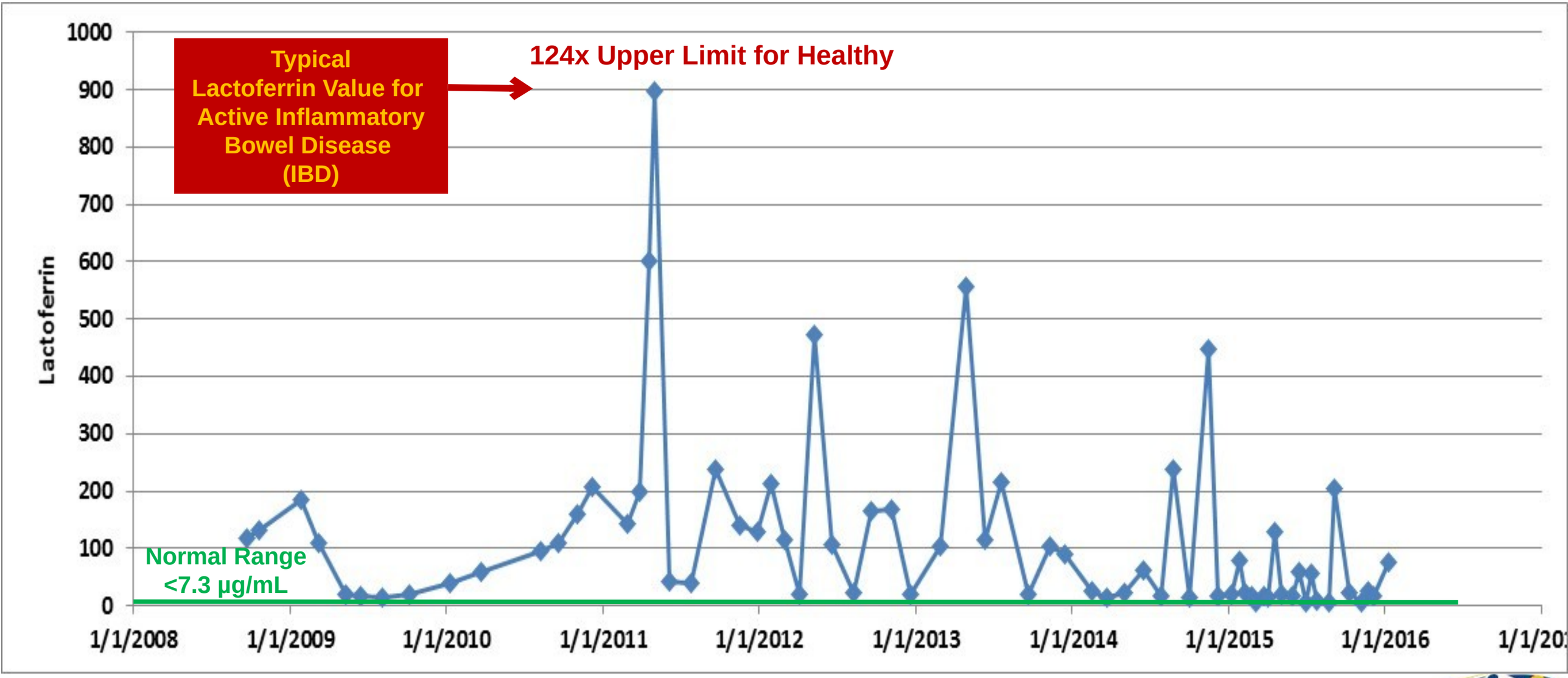
My Quarterly Blood Draw

Only One of My Blood Measurements Was Far Out of Range--Indicating Chronic Inflammation



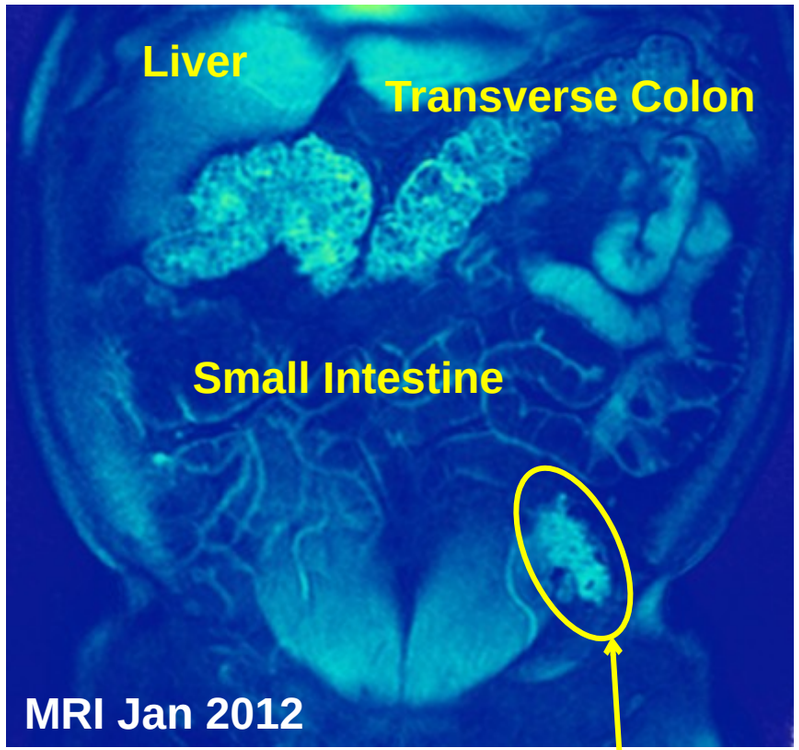
Complex Reactive Protein (CRP) is a Blood Biomarker for Detecting Presence of Inflammation

Longitudinal Stool Tests Revealed Large Excursions in My Immune System: Inflammatory Bowel Disease (IBD)



Lactoferrin is a Protein Shed from Neutrophils - An Antibacterial that Sequesters Iron

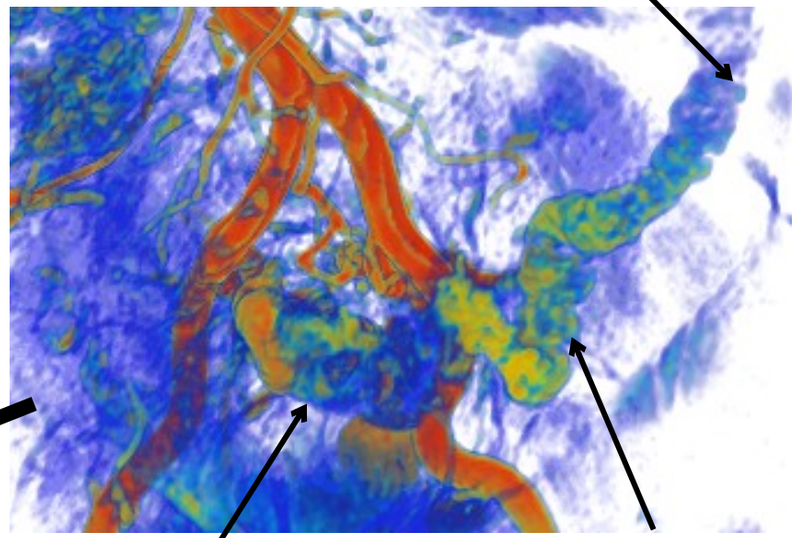
Confirming the IBD (Colonic Crohn's) Hypothesis: Finding the "Smoking Gun" with MRI Imaging



MRI Ordered
By Dr. Bill Sandborn;
MRI Read by
Dr. Cynthia Santillan
UCSD

I Obtained the MRI Slices From UCSD Medical Services and Converted to Interactive 3D Working With Calit2 Staff

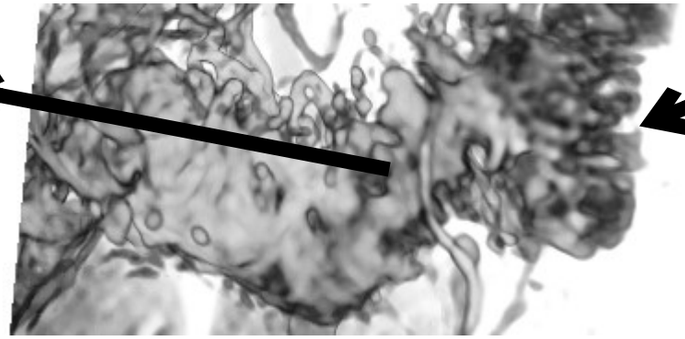
Descending Colon



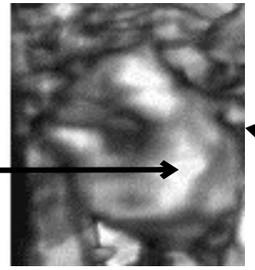
Major Kink

Sigmoid Colon
Threading Iliac Arteries

Diseased Sigmoid Colon



Cross Section

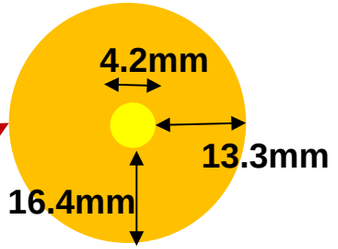


Severe Colon
Wall Swelling

2016 MRI Slice Through Sigmoid Colon Reveals Thick Walls and Very Narrow Lumen



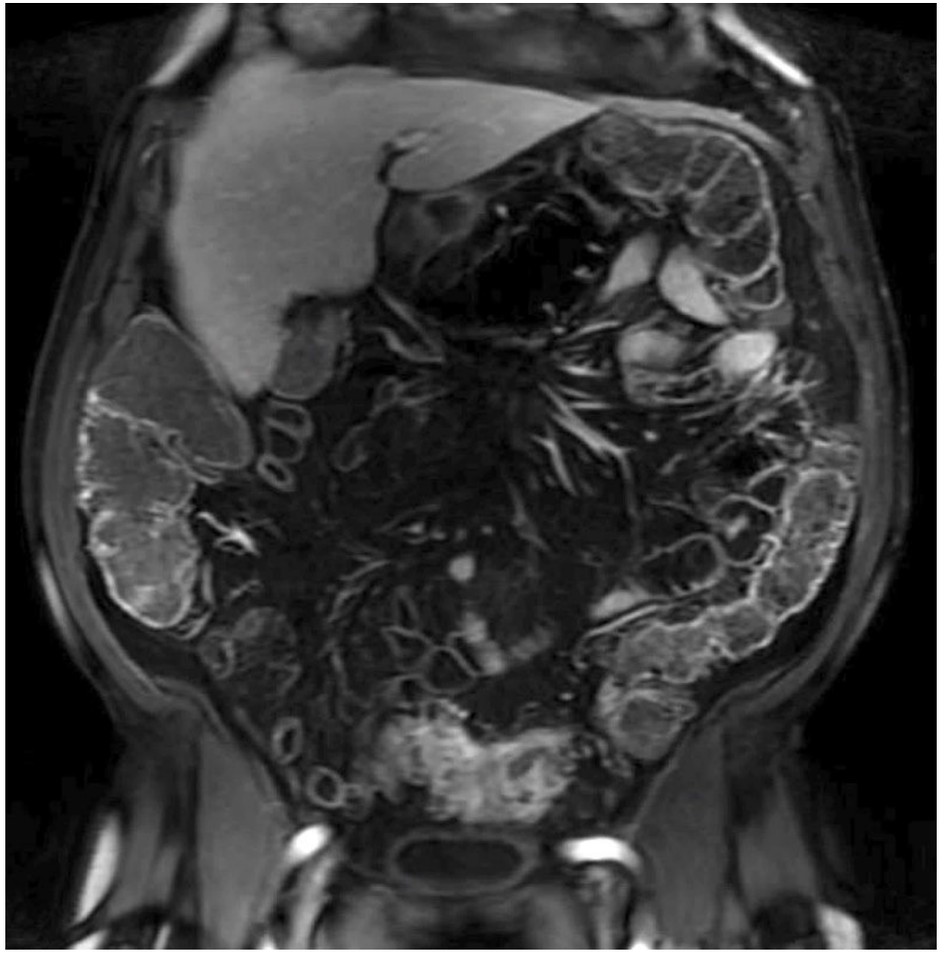
Source: Smarr MRI Oct. 25, 2016
Reading by Cynthia Santillan,
MD Radiologist, UCSD



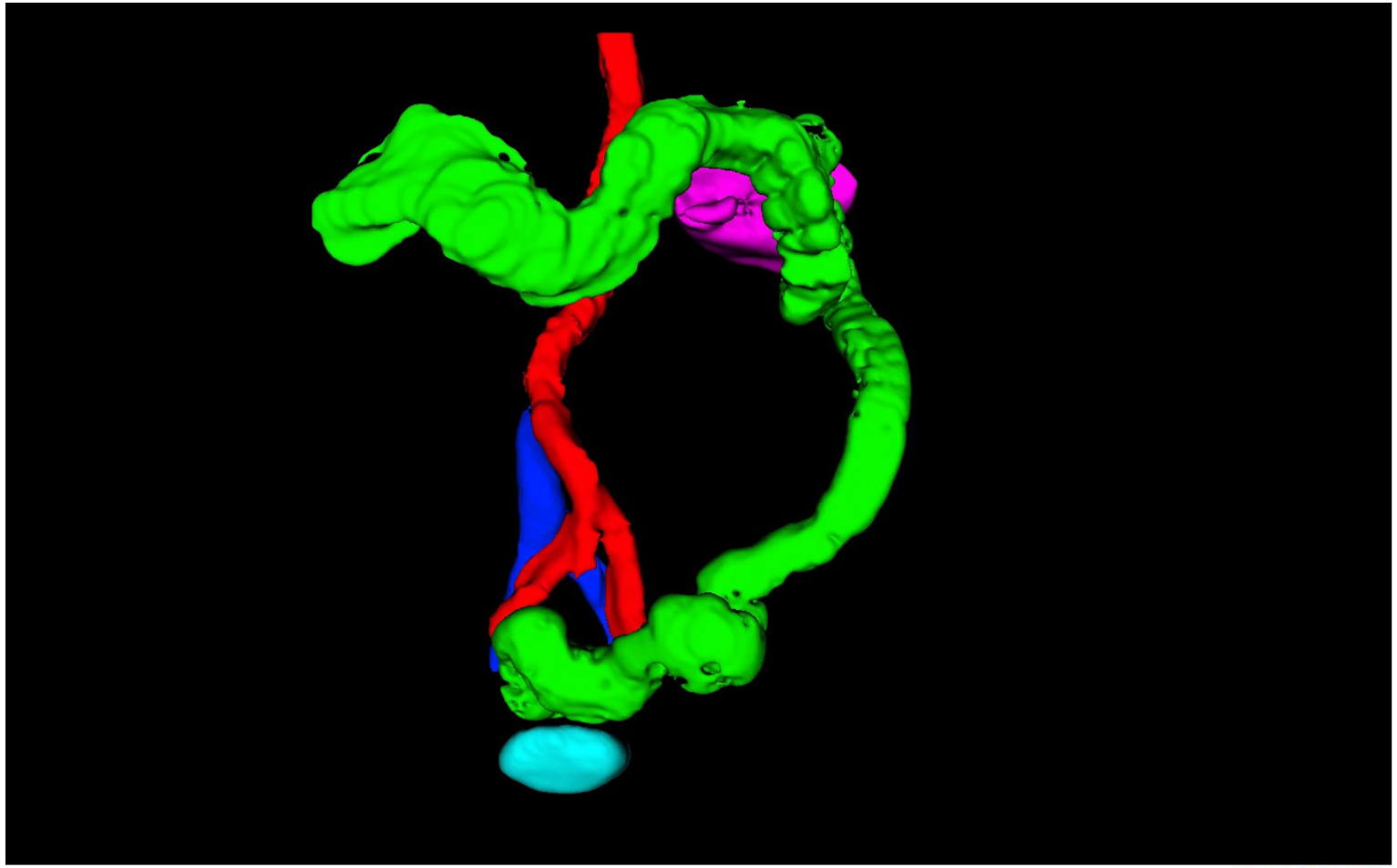
Normal opening (bright yellow) is 40mm, so mine is 1/10 the diameter it should be.

Normal wall thickness (dark yellow) is 3mm, so wall thickness is 4-5 times as thick as it should be.

My Team Converted Abdominal MRI Slices to 3D Organ Segmentation for Surgical Pre-Planning



MRI Slice from Dr. Cynthia Santillan



3D Organ Segmentation Made by Dr. Jurgen Schulze from Dr. Santillan's 150-Slice MRI

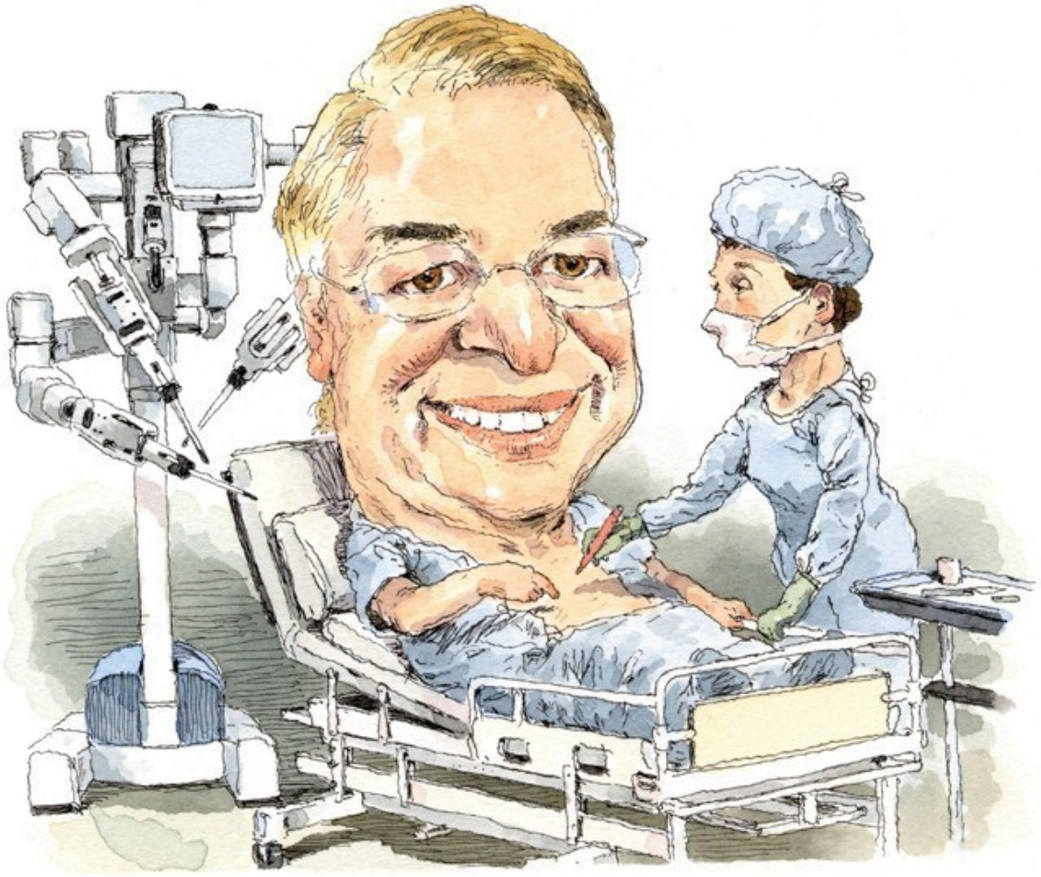
The Ability to See Inside Myself Led to My Co-Planning My Own Surgery

The Atlantic

The Man Who Saw Inside Himself

For years, Larry Smarr has used a supercomputer to monitor his health and peer at his organs. Recently, he used his knowledge to help direct his own surgery.

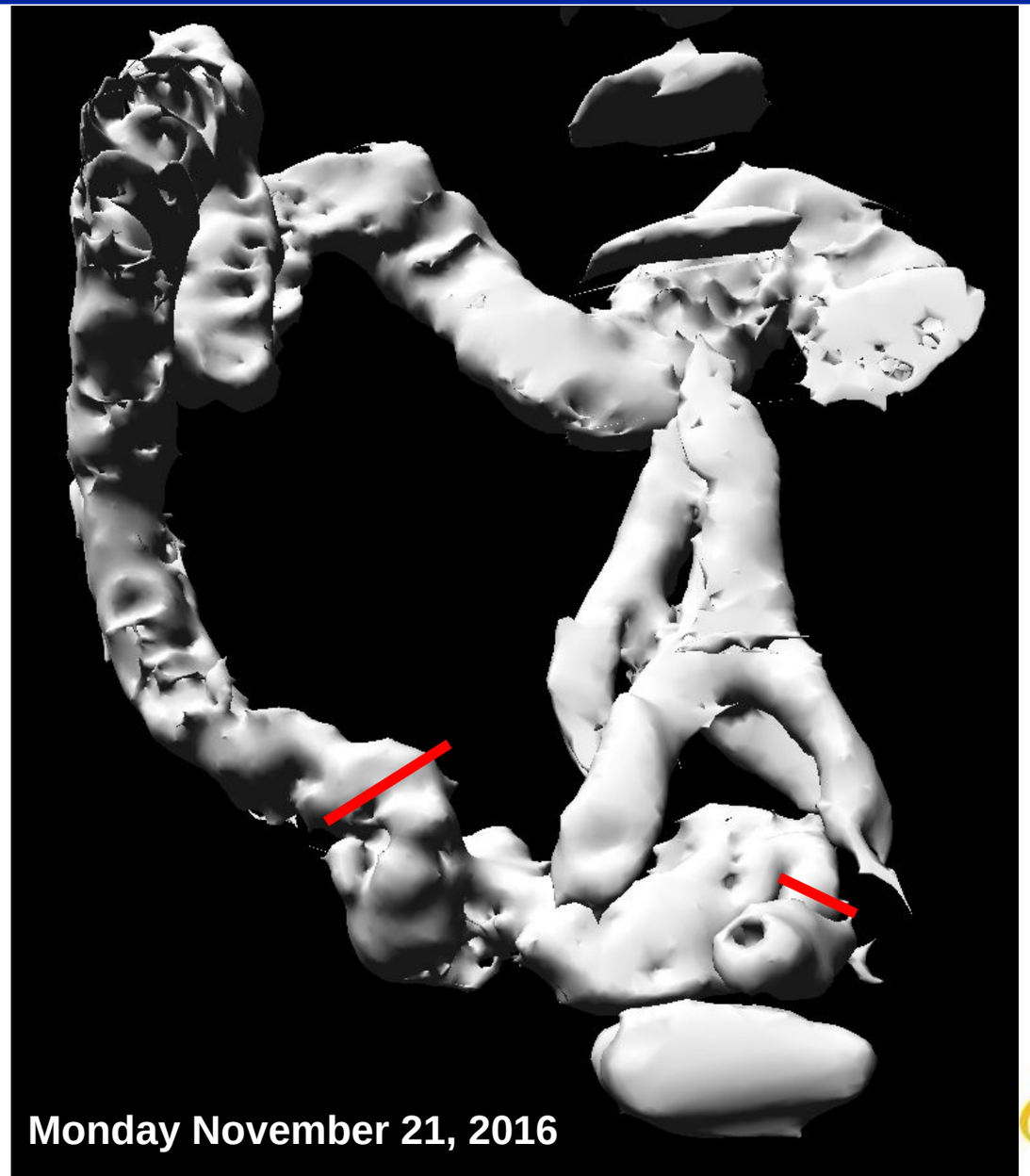
MARK BOWDEN | MARCH 2018 ISSUE | HEALTH



Pre-Surgical Planning in QI Virtual Reality:
Using Virtual Reality As Input for Positioning The Two Resection Cuts



Colon visualization by Jurgen Schulze, Calit2;
Photo credit Tom DeFanti, Calit2

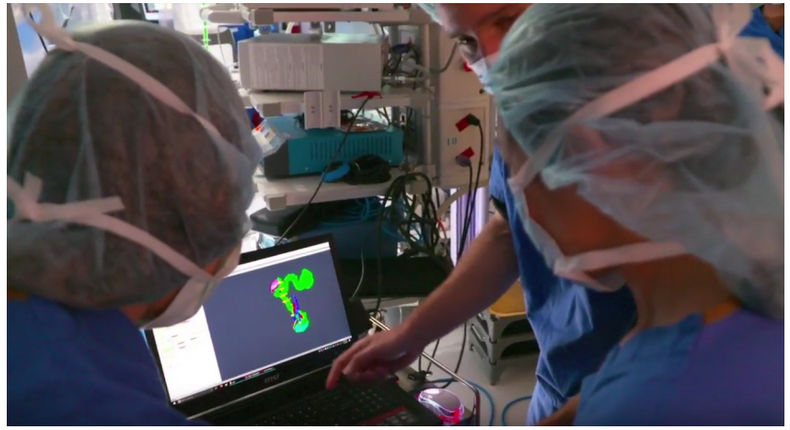


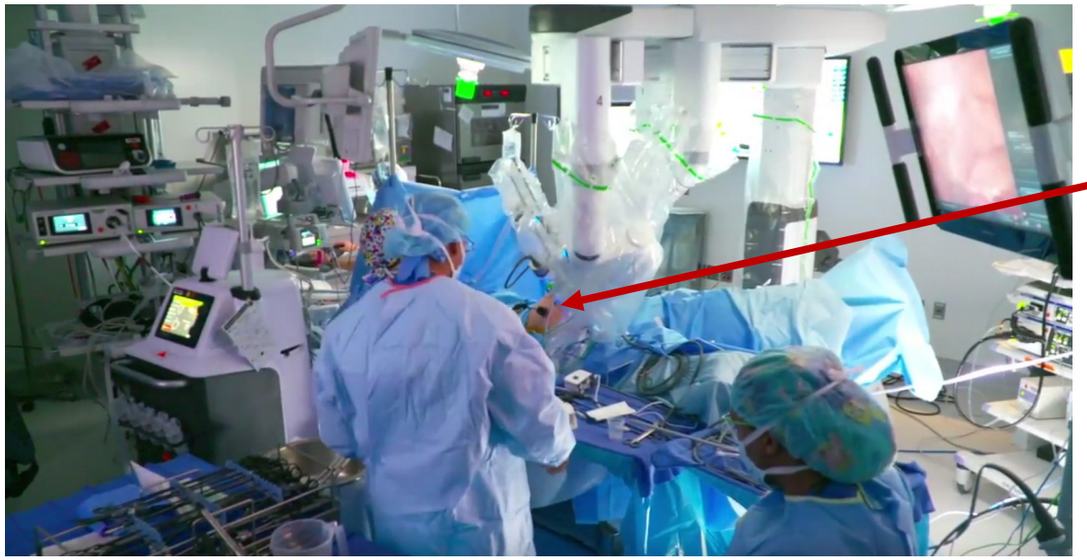
Dr. Kurisu Prescribed Pre-Surgery Mental/Emotional Preparation Over Thanksgiving 2016



Using Calit2 Organ Segmentation During My Sigmoid Colon Resection Surgery

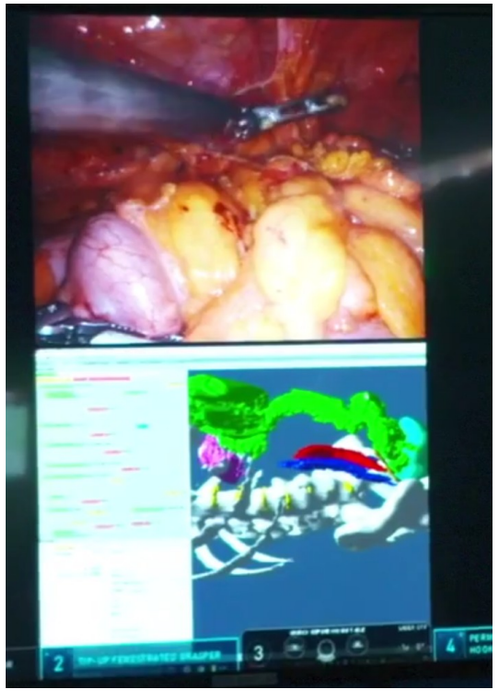
Dr. Schulze Rotating 3D Organs To Match Up With da Vinci Arms and Internal Camera





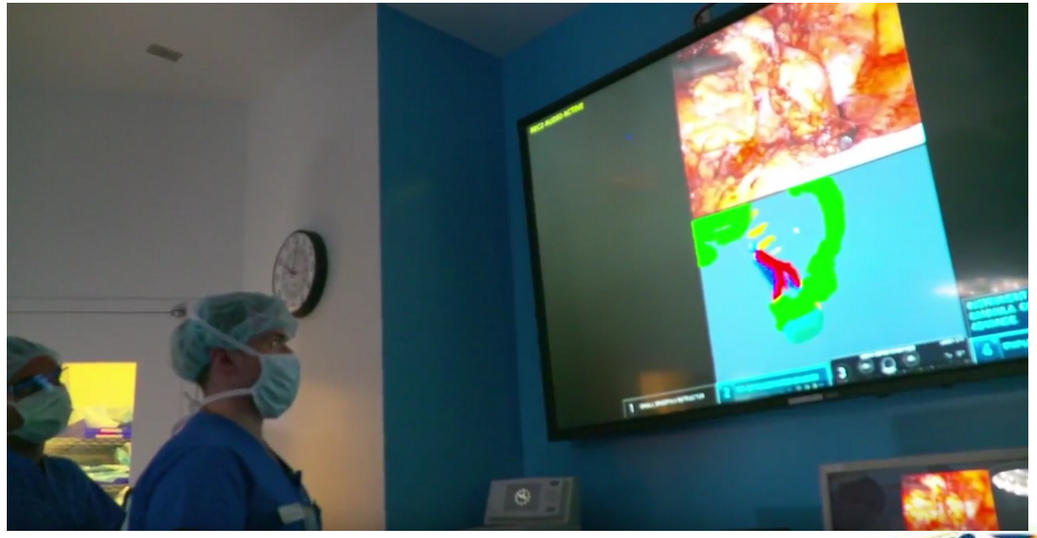
Patient Smarr With da Vinci Robot Arms Inside Him

Tuesday November 29, 2016





Dr. Ramamoorthy Operating Da Vinci Xi Robot During Surgery



OR Team Using Large Screens To Watch Dr. Schulze's da Vinci Images

Surgery Day:
Worlds Apart Yet Connected

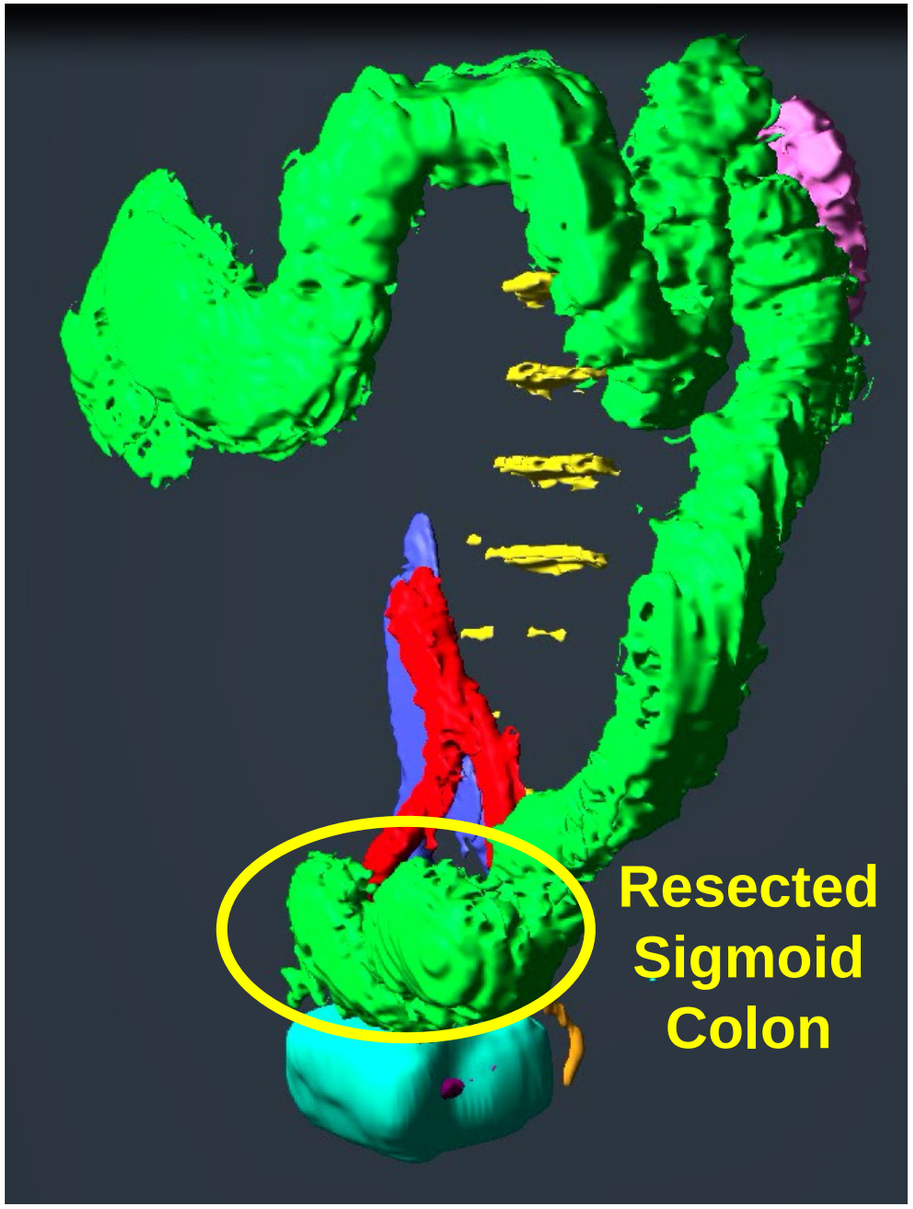


Dr. Smarr



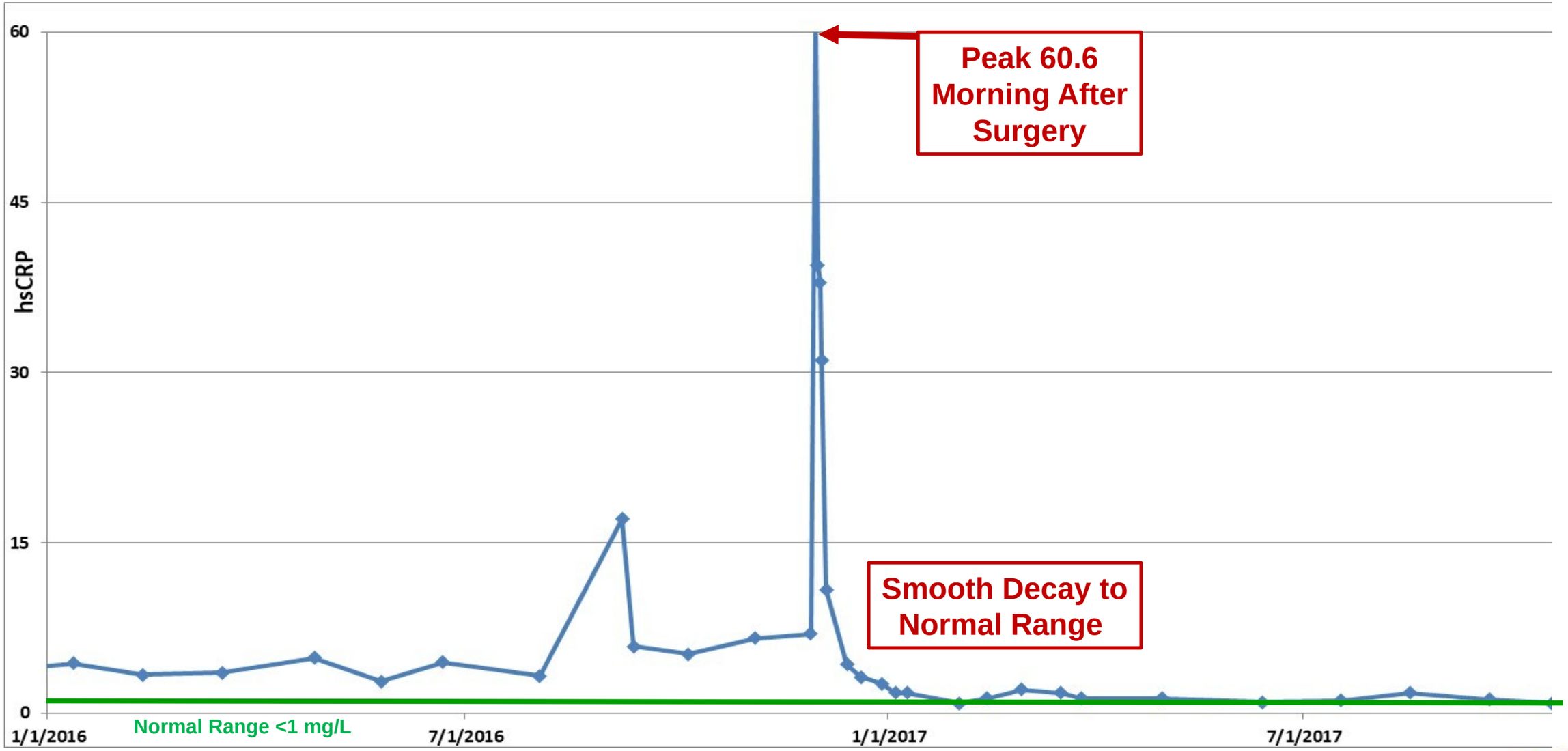
Dr. Kurisu

3D View of Colon
Before and After Surgery

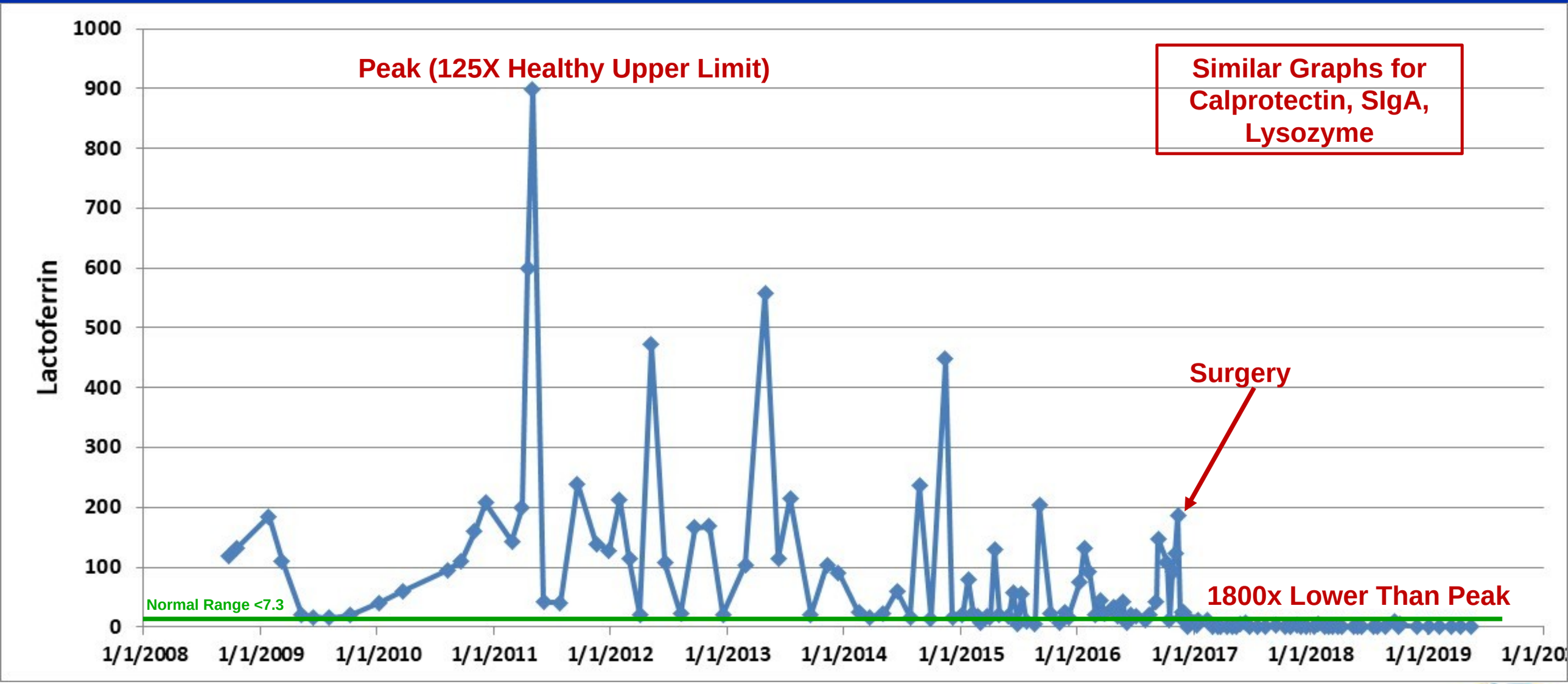




Using hsCRP Daily Time Series Following Surgery to Detect Post-Surgical Complications



Colonic Inflammation:
Abrupt Shift to Healthy Following Surgical Resection



Dr. Hollis King's Osteopathic Visceral Manipulation Dissolved All My Postoperative Adhesions

The Journal of the American Osteopathic Association
Established 1901

Abdominal Visceral Manipulation Prevents and Reduces Peritoneal Adhesions

January 2013

Michael A. Seffinger, DO; Amy Jemelka Martin, OMS IV



I Have Had 33 Half-Hour OMT Sessions With Hollis
Since March 29, 2017
Including Cranial and Vagal OMT

Time Series Reveals Behavior Changes (Depression, Malaise) Associated with Time Progression of Autoimmune Disease



Immune & Inflammation Variables

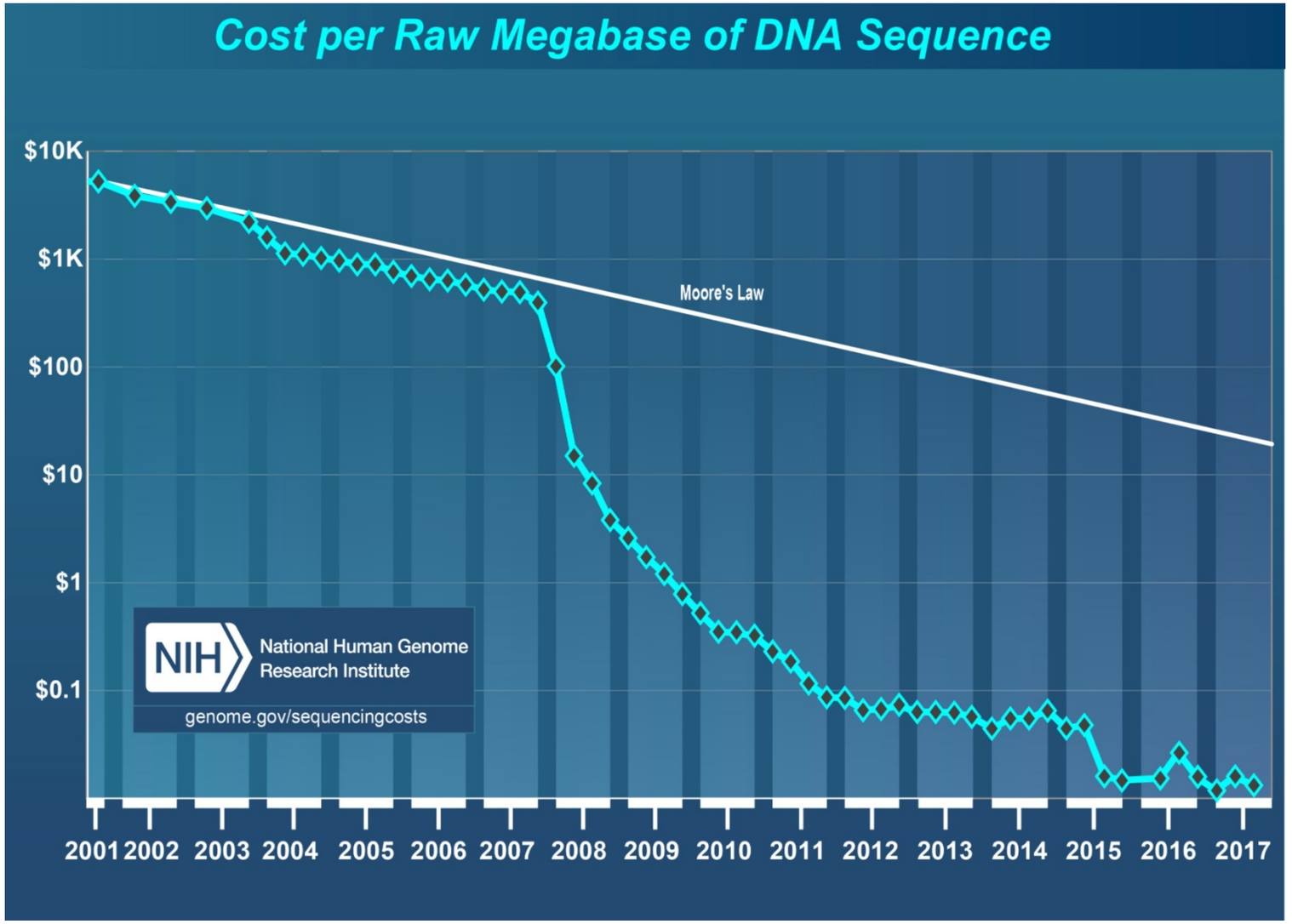
Weekly Symptoms

Mood Disorders

Pharma Therapies Stool Samples

To Understand Episodic Depression
One Needs to Sequence My Stool Samples
To Reveal Gut Microbiome Ecology Dynamics

Analysis of the Microbiome Is Becoming Possible Because The Cost of Sequencing DNA Has Fallen Over 100,000x in the Last Ten Years



This Has Enabled a "Golden Age" of Discovery in Both Human and Microbiome Genetics

The Patient's Body
Includes a Vast Number of Microbes

Your Body Has 10 Times
As Many Microbe Cells As Human Cells

Your Microbiome is
Your "Near-Body" Environment
and its Cells
Contain 300x
as Many DNA Genes
As Your Human Cells

When We Think About Biological Diversity
We Typically Think of the Wide Range of Animals






But All These Animals Are in One SubPhylum Vertebrata of the Chordata Phylum

All images from Wikimedia Commons.
Photos are public domain or by Trisha Shears & Richard Bartz

Think of These Phyla of Animals When You Consider the Biodiversity of Microbes Inside You



Phylum Chordata



Phylum Cnidaria



Phylum Echinodermata



Phylum Annelida



Phylum Mollusca



Phylum Arthropoda

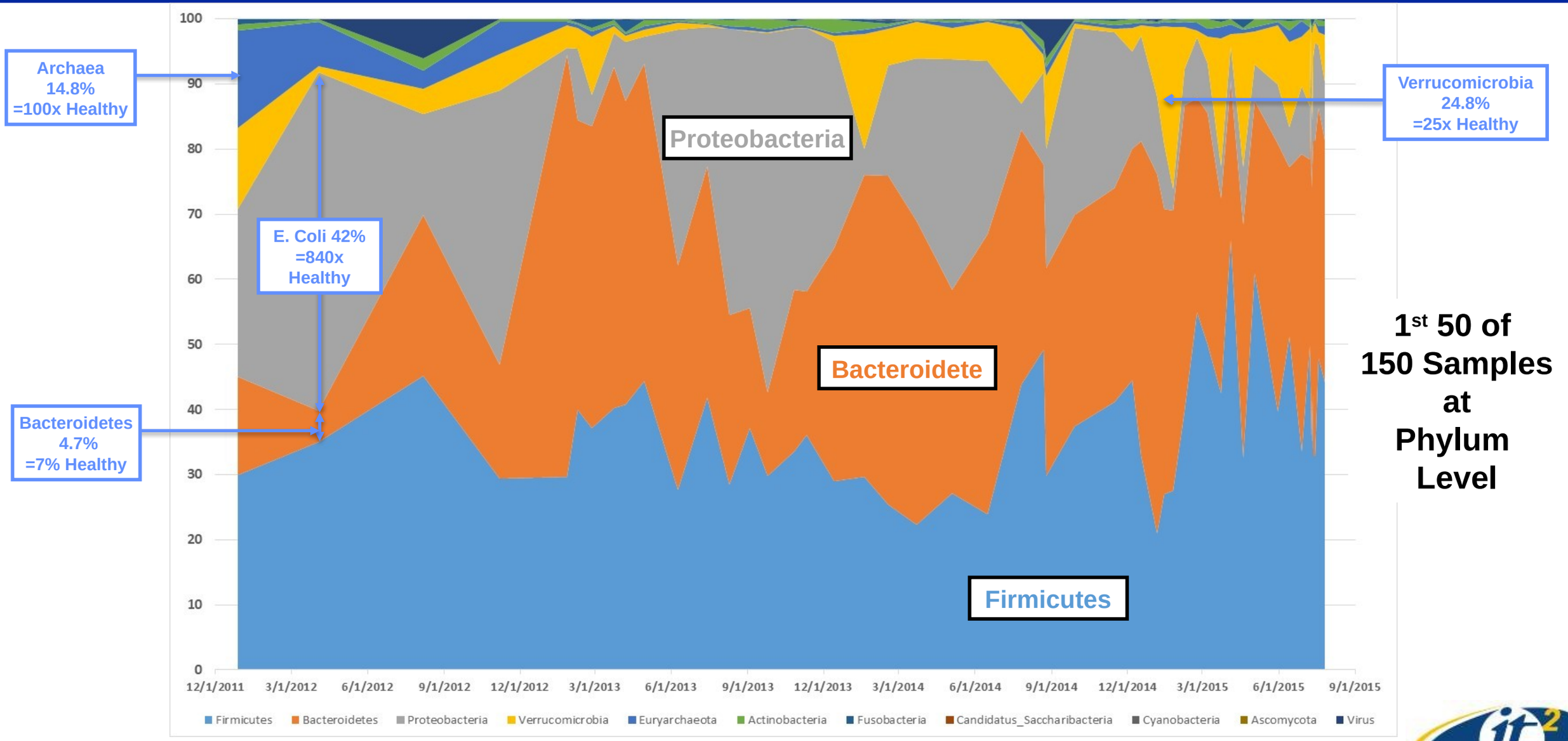
Microbiome Phyla

- Bacteroidetes
- Firmicutes
- Proteobacteria
- Verrucomicrobia
- Actinobacteria
- Fusobacteria
- Euryarchaeota

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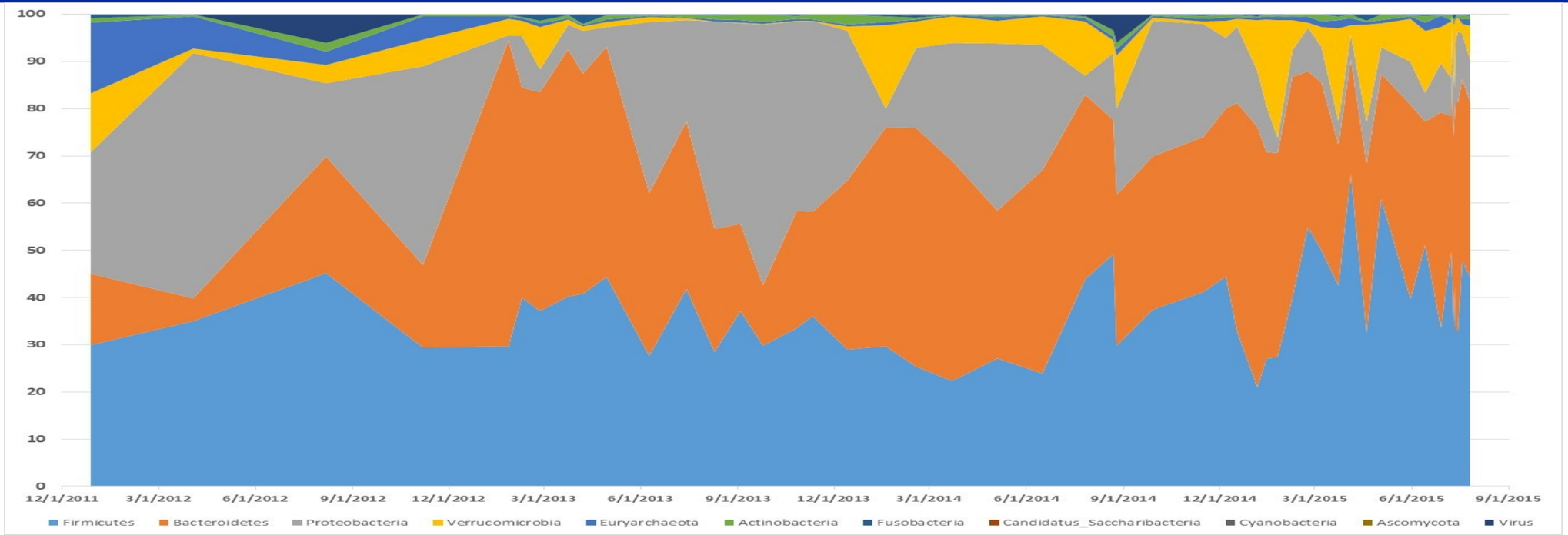
Metagenomically Sequencing Long Time Series Stool Samples to Reveal Patient Gut Microbiome Ecology Dynamics During Disease

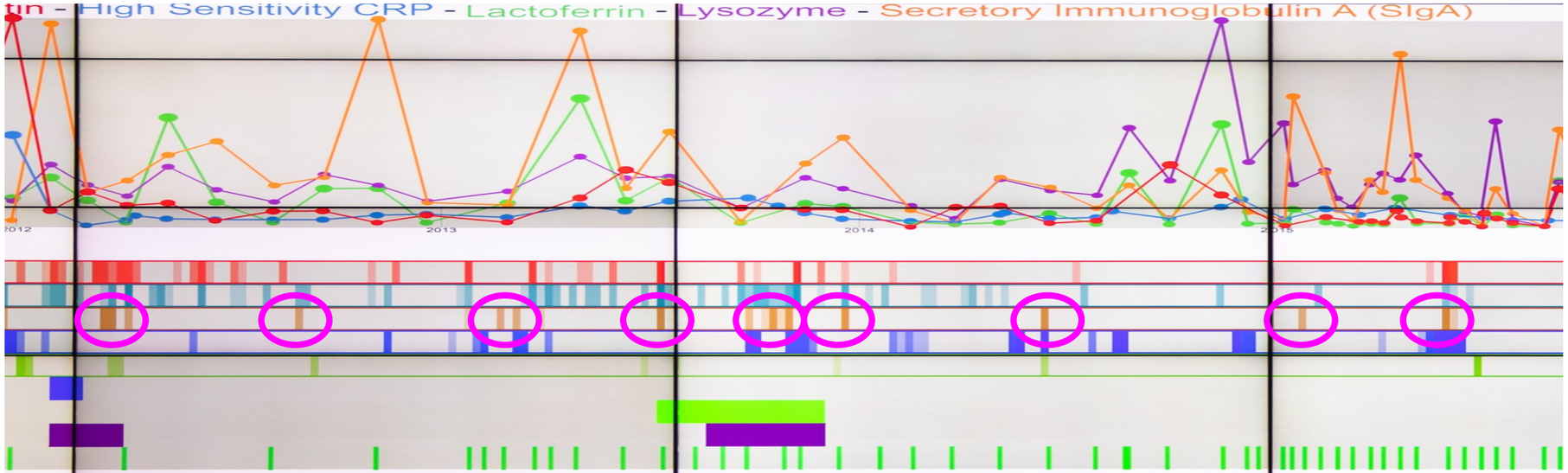


1st 50 of 150 Samples at Phylum Level

Sequencing Rob Knight Lab; Analysis Xin Fang, UCSD

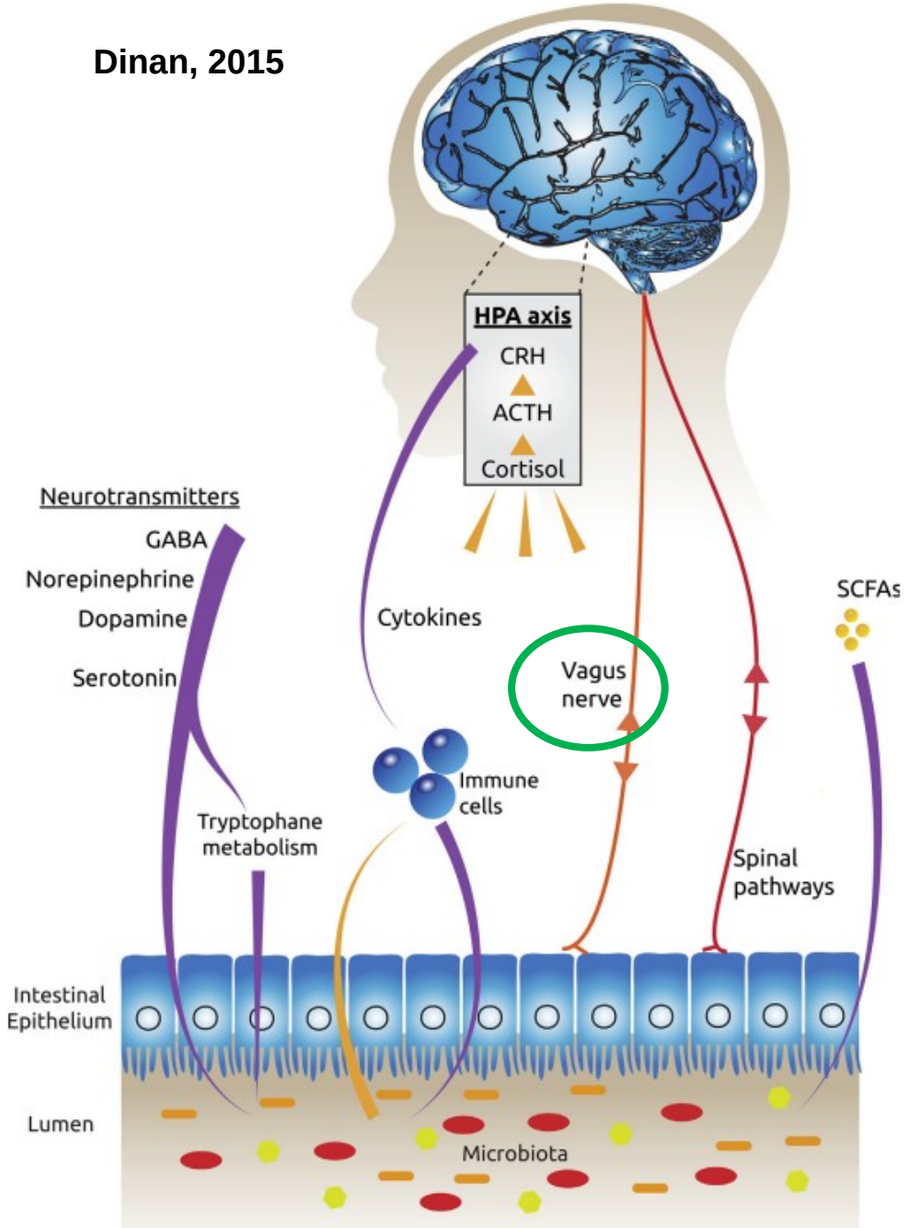
First Alignment of Microbiome Ecology with Inflammation and Immune Biomarkers, Pharma, and Symptoms

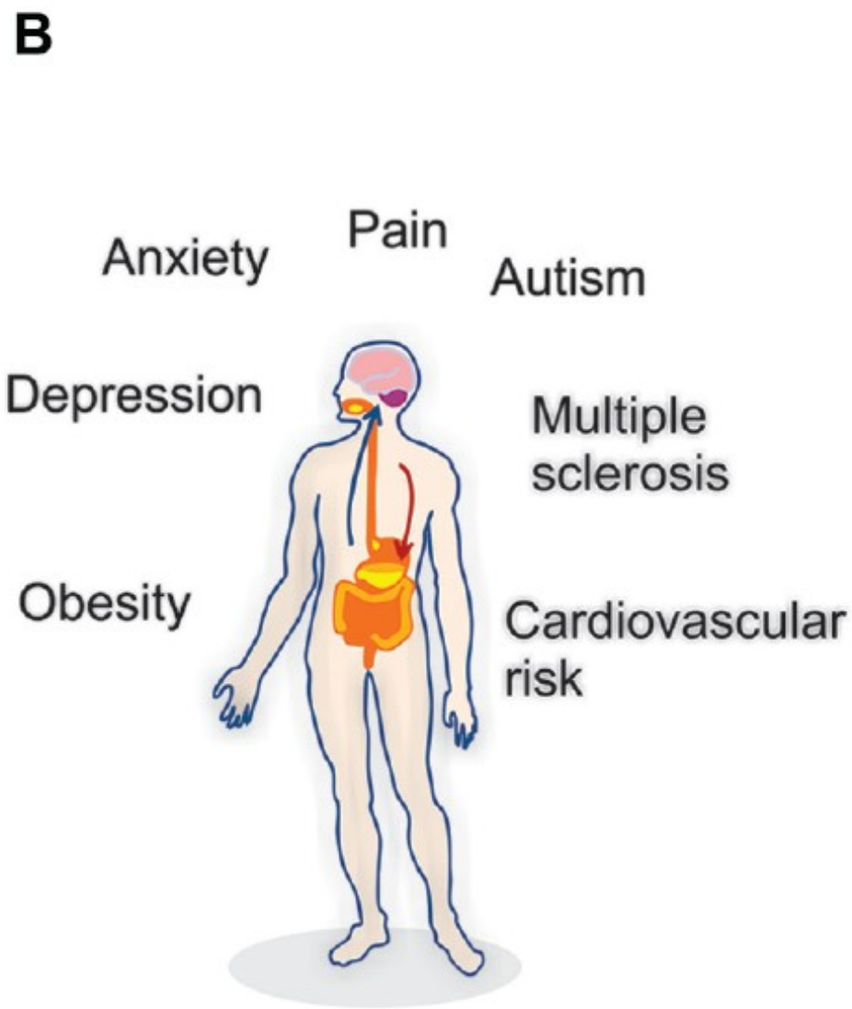




The Microbiome–Gut–Brain Axis Provides New Systemic Insights into Shifts in Behavior and Disease

Dinan, 2015





Source: Montiel-Castro, et al.
Frontiers in Integrative Neuroscience 2013

Gut Microbes Regulate Serotonin Production, 90% of Which is in the Large Intestine

AMERICAN PSYCHOLOGICAL ASSOCIATION

**“It's almost unthinkable
that the gut is not playing a critical role in mind states,"
says gastroenterologist Emeran Mayer, MD,
director of the Center for Neurobiology of Stress at UCLA**

By Dr. Siri Carpenter
September 2012, Vol 43,

"More and more studies are showing that mice or other model organisms with changes in their gut microbes exhibit altered behaviours," noted senior author Dr Elaine Hsiao of Caltech.

***Cell* 161 264-276 (2015)**

AMI American Microbiome Institute

April 13, 2015

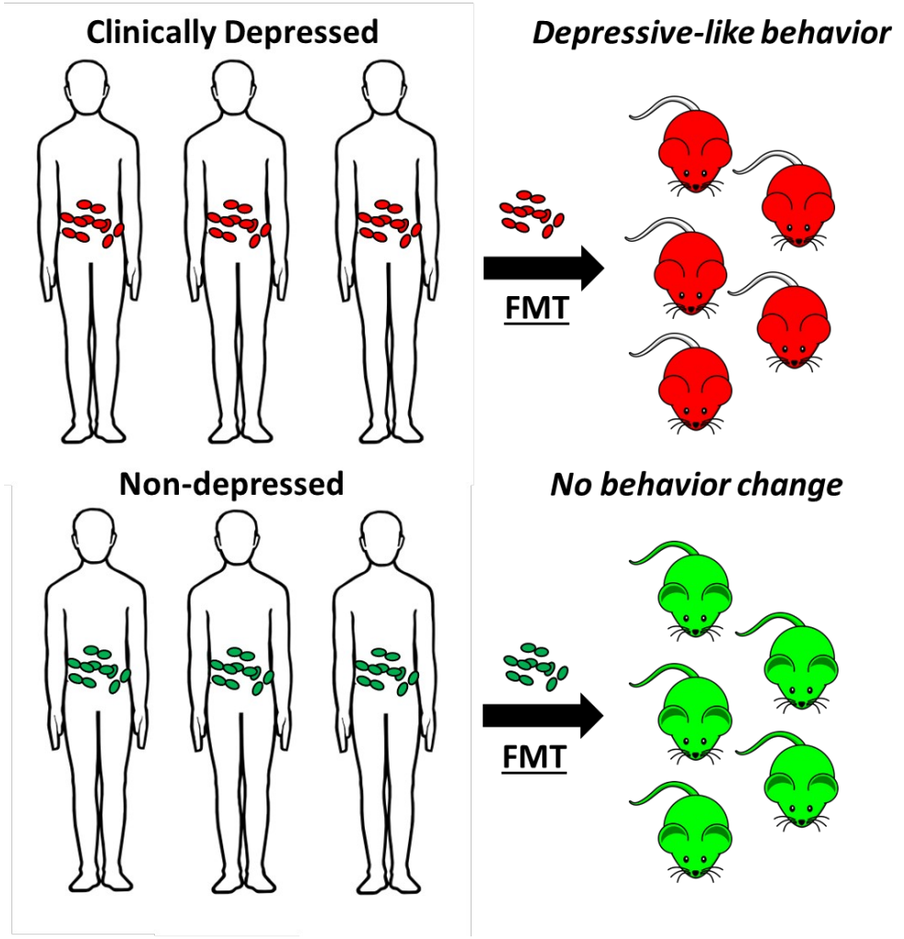
Gut bacteria help regulate serotonin levels

The Gut Microbiome and Mental Health

- **The Microbiome is Linked to Many Components of Mental Health**
  - Brain Development
  - Mood/Behavior
  - Neurodegenerative Disorders

- **Comorbidity is Common Between CNS and GI Disorders**

- **Antibiotics Use Has Been Linked To Behavioral Phenotypes (Depression + Anxiety)**
  - But Not Antivirals or Antifungals



Fecal Microbiome Transplant from Human to Animal Transmits Phenotype

Source: Jack Gilbert, UCSD

Gut Microbiome Dysbiosis
Is Being Linked to Irritable Bowel Syndrome and Depression

GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

The Role of Gut-Brain Interactions in Influencing Symptoms of Irritable Bowel Syndrome



Emeran A. Mayer, MD, PhD
Director, G. Oppenheimer Center for Neurobiology of Stress & Resilience
UCLA Vatche and Tamar Manoukian Division of Digestive Diseases
UCLA Microbiome Center
Los Angeles, California

January 2018

Viewpoint | Free Access

Melancholic microbes: a link between gut microbiota and depression?

T. G. Dinan, J. F. Cryan

Neurogastroenterology & Motility

01 August 2013

EDITORIAL · 04 FEBRUARY 2019

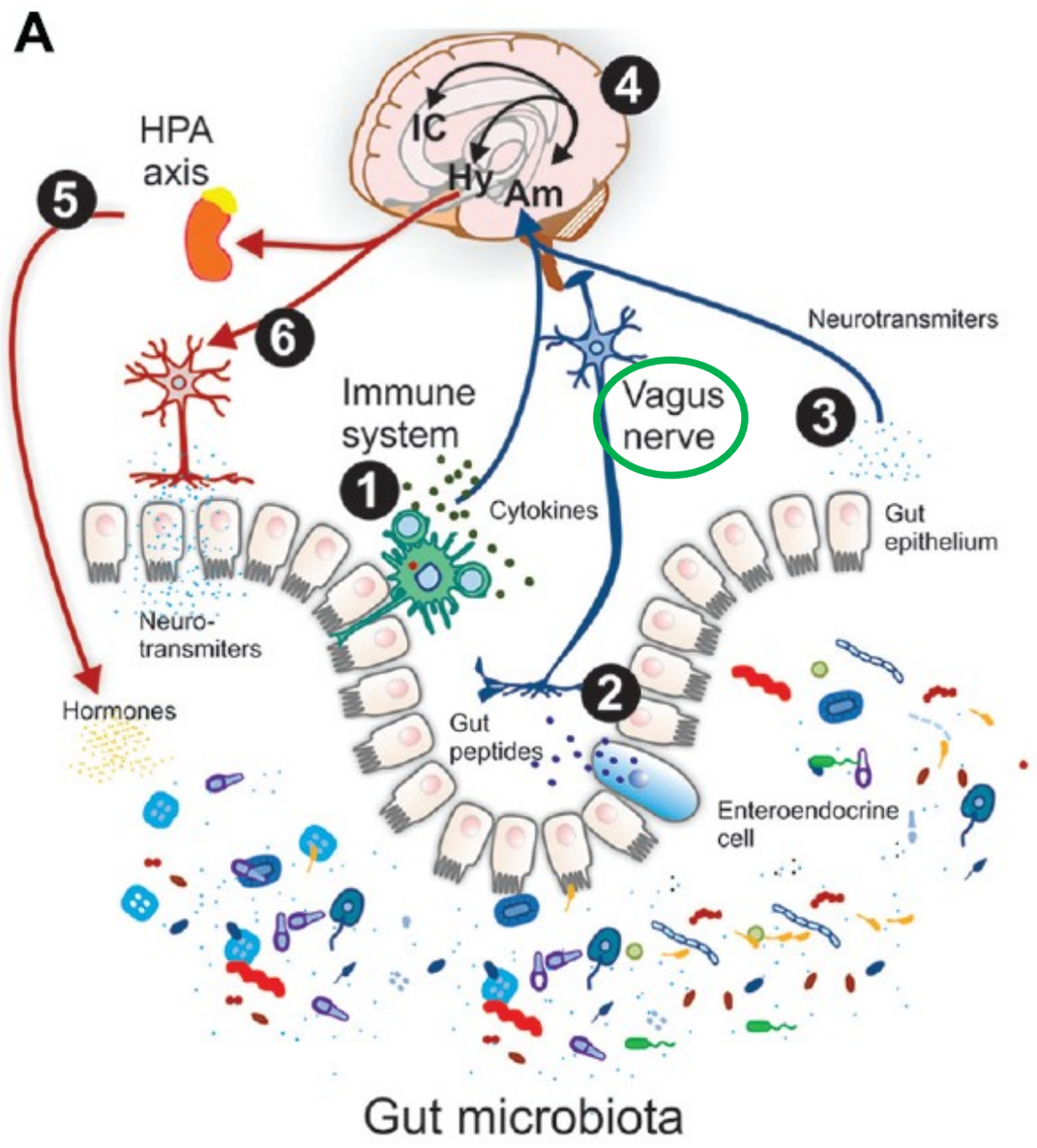
Links between gut microbes and depression strengthened

The once-wild idea that intestinal bacteria influence mental health has transformed into a major research pursuit.

nature
International journal of science

Manipulating the Vagus Nerve Has Impacts Throughout the Body

Source: Montiel-Castro, et al.
Frontiers in Integrative Neuroscience 2013

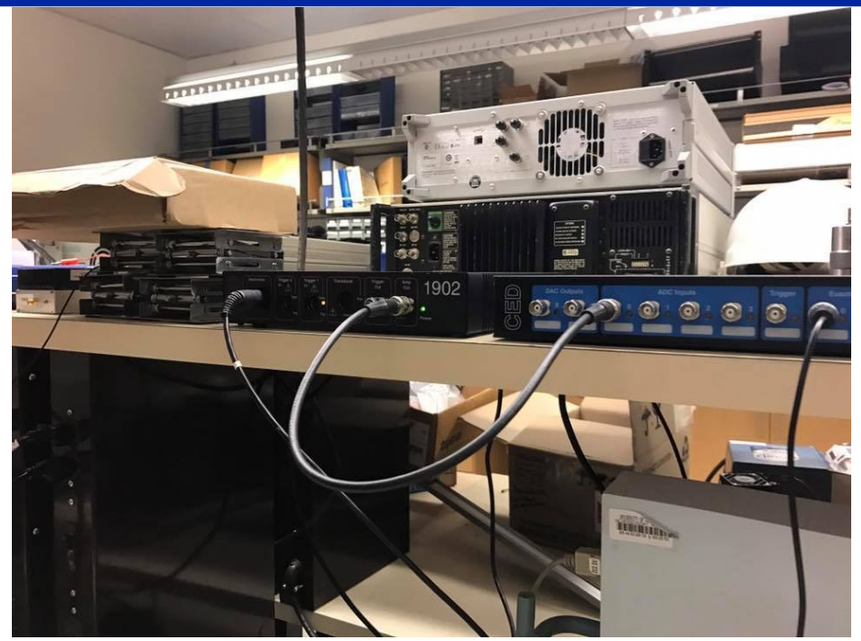


Calit2 is Applying Engineering to Manipulating the Vagus Nerve

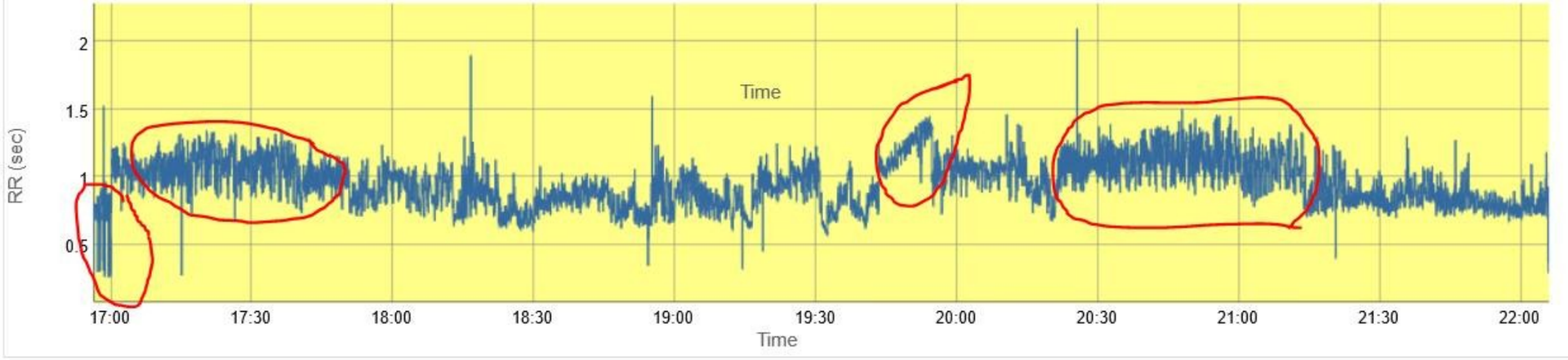


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Modulating the Vagus Nerve with a Flexible Comfortable Ultrasound Array





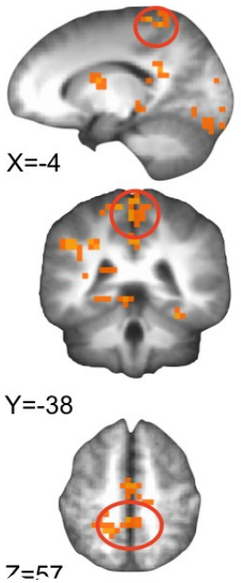


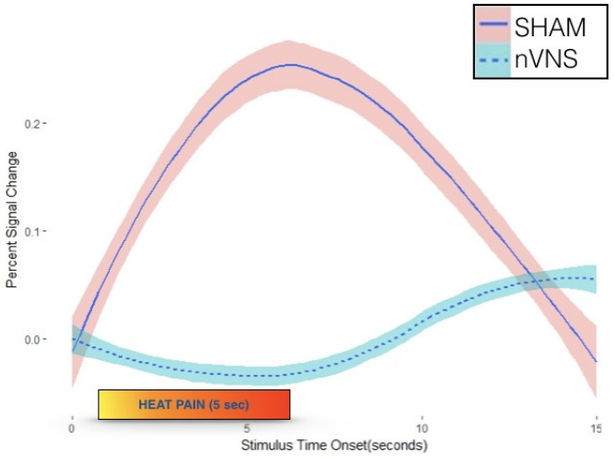
Ultrasound

Meditation

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Transcutaneous Vagus Nerve Stimulation (tVNS) Blocks Sensory Pain and Emotional Pain





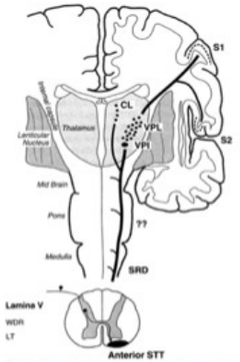
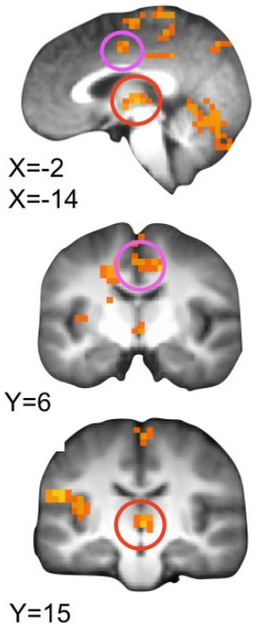
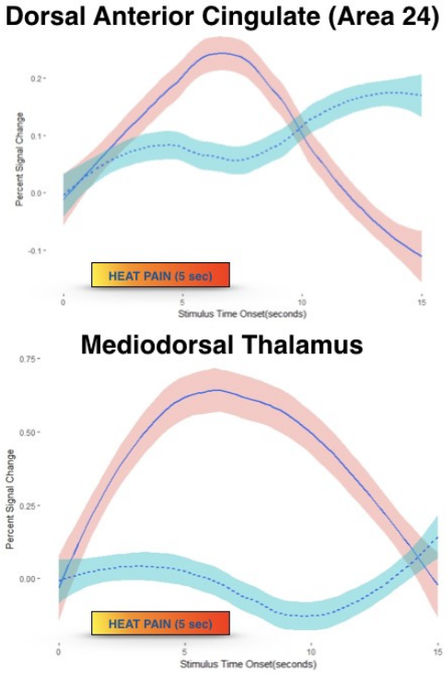


Fig. 10.3. Schematic diagram summarizing the ascending projections of laminas IV–V cells in the macaque monkey. The axons of both low-threshold (LT) and wide dynamic range (WDR) cell types decussate and ascend in the anterior STT. Terminations occur in the brainstem in the subnucleus reticularis dorsalis (SRD) and other sites, probably including the reticular core. In the thalamus, laminas IV–V STT terminations occur in VPI, in VPL, in VL and in CL. (Reproduced from Craig and Dostrovsky, 1999, with permission from Elsevier.)

We Can Use These Technologies To Study The Impact of OMT





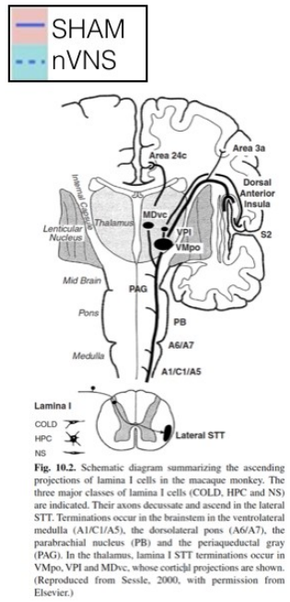


Fig. 10.2. Schematic diagram summarizing the ascending projections of lamina I cells in the macaque monkey. The three major classes of lamina I cells (COLD, HPC and NS) are indicated. Their axons decussate and ascend in the lateral STT. Terminations occur in the brainstem in the ventrolateral medulla (A1/C1/A5), the dorsolateral pons (A6/A7), the parabrachial nucleus (PB) and the periaqueductal gray (PAG). In the thalamus, lamina I STT terminations occur in VMpo, VPI and MDvc, whose cortical projections are shown. (Reproduced from Sessle, 2000, with permission from Elsevier.)

Bilateral Primary Somatosensory Cortex (SI)
Lateral Pain Pathway
Sensory Pain

Anterior Cingulate (Area 24)
Mediodorsal Thalamus
Medial Pathway
Emotional Unpleasantness of Pain

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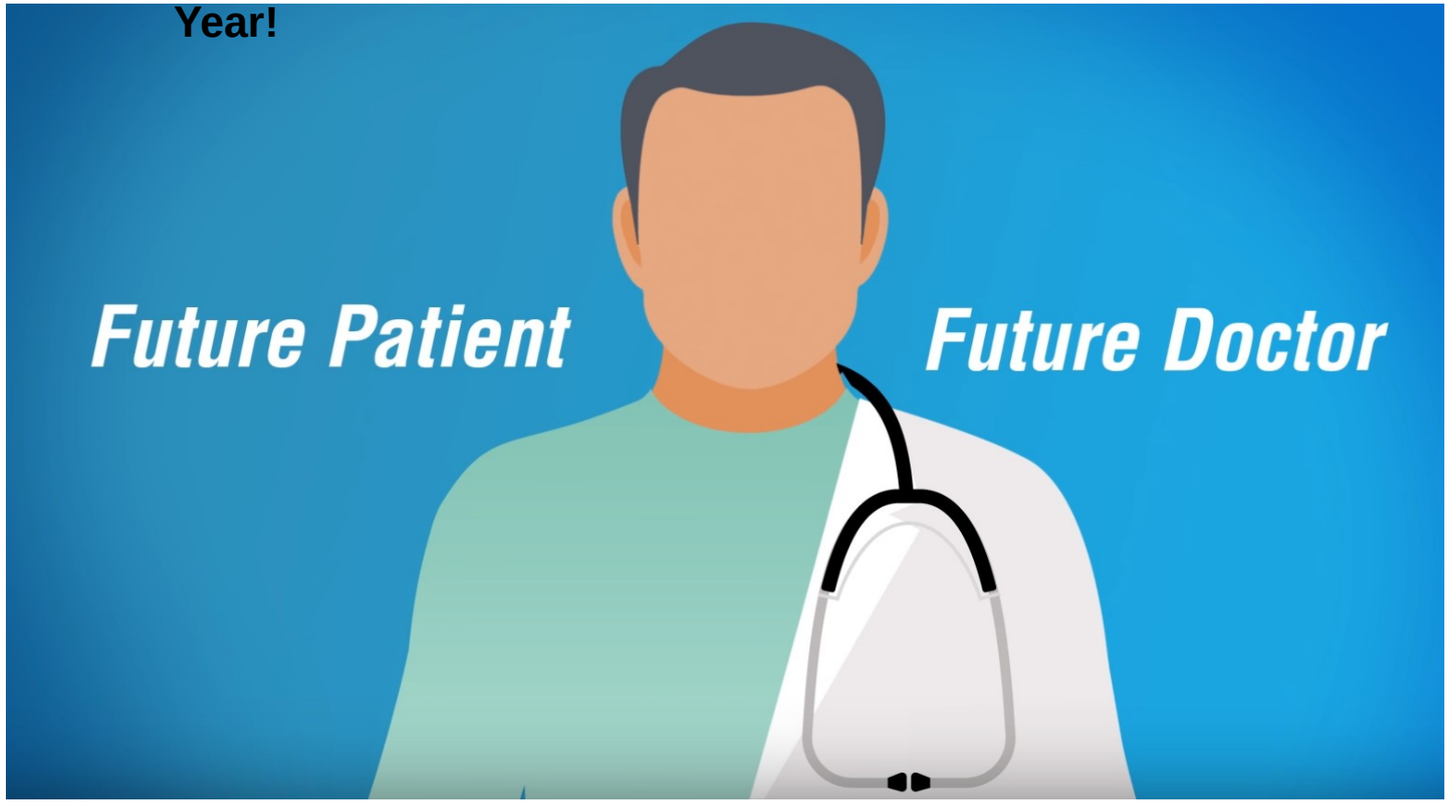
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