

Fusion

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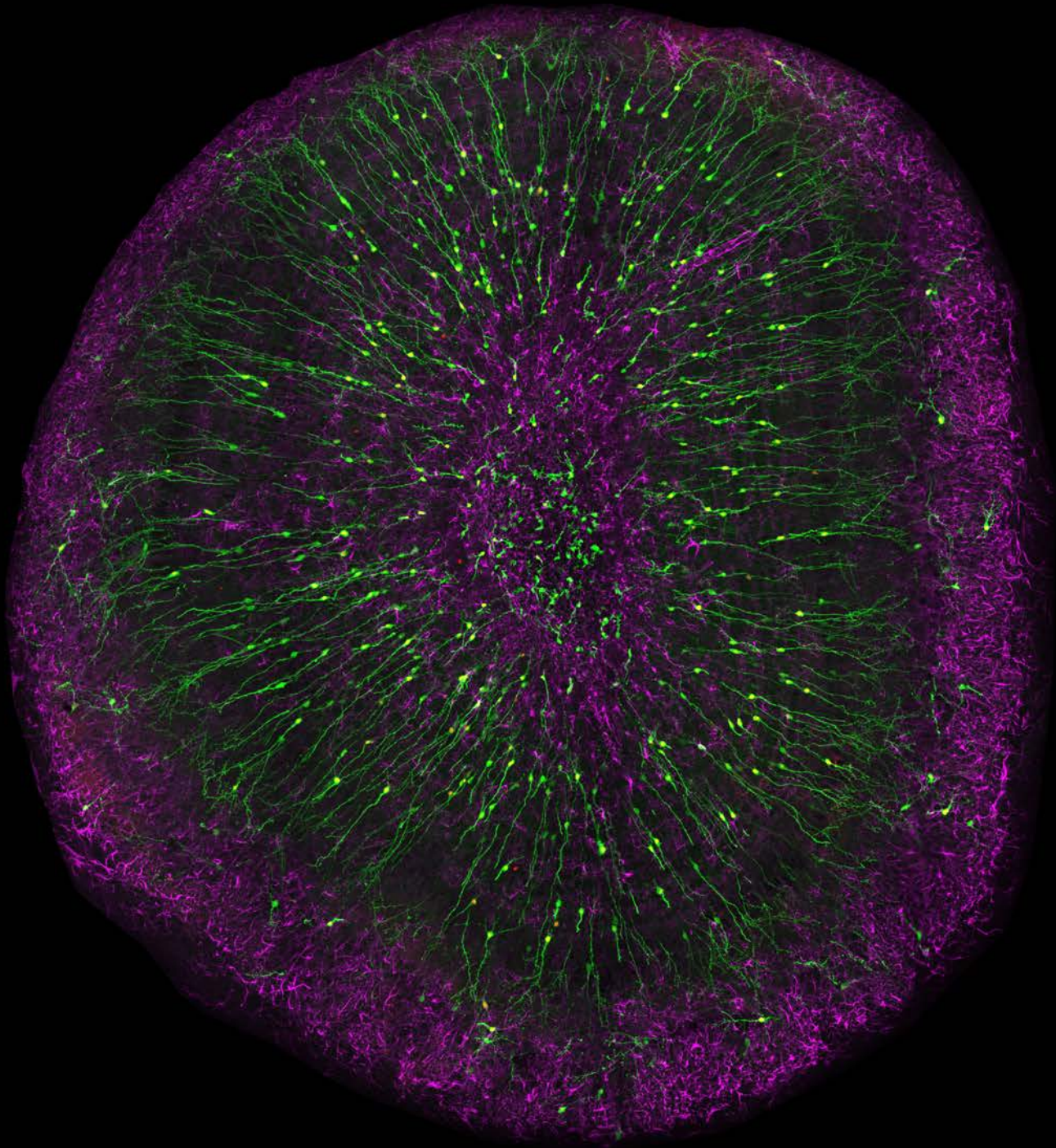


Table of Contents:

WILLIAM H. BEAUMONT RESEARCH PRIZE WINNERS

Nicole Casasanta and Sarit Toltzis, Relationship of Hereditary Cancer Syndromes and Oncotype DX Recurrence Score. . p. 6

Dara Baker, The Role of DFMO in Helicobacter Pylori Infection: Modulation of ROS Response p. 7

Christina Pugliese, Etiology and Management of Hospitalized and Outpatient Diarrhea Among Children Less Than 5 Years of Age in Lambaréné, Gabon. p. 9

ON THE COVER

This year, the George Washington University School of Medicine and Health Sciences (SMHS) hosted its first-ever Art of Science Contest. Looking at the image gracing the cover of Fusion, one might not know the bright purple and green colors represent olfactory bulb interneurons and astrocytes in the brain, but that's the beauty of art: there's more to it than meets the eye.

The image came from grand prize winner first-year MD student Aslam Akhtar, PhD, who said a push from classmates and class discussions about the olfactory bulb neurons – the neurons responsible for our sense of smell – led him to enter his image in the contest.

The four contest winners – chosen by a team of SMHS deans, students, and staff – will have their images displayed in the SMHS Dean's Suite in Ross Hall.



BASIC SCIENCE

Alex Gu, Alterations to Maternal Cortical and Trabecular Bone in Multiparous Middle-Aged Mice p. 11

Julia Buldo-Licciardi, Secretomic Analysis of Spent Embryo Culture Media p. 12

CLINICAL RESEARCH

Adam J. Michalak, Efficacy of Manipulation under Anesthesia for Stiffness Following Total Knee Arthroplasty: A Systematic Review. p. 14

Alexa Lean, Efficacy of Outpatient Ketamine Infusions on Different Etiologies of Chronic Pain p. 16

Alysia Wiener, A Phase II Study of Copper-Depletion Using Tetrathiomolybdate in Patients with Breast Cancer at High Risk for Recurrence: Updated Results p. 17

Chloe Harrington, Effect of Demographic and Psychological Factors on 12 Month Outcomes in Adolescent Bariatric Surgery p.18

Danny Lee, Effect of Genetic Variation in GSTP1 and AXIN1 on Bone Mineral Density in Children and Young Adults p. 19

David Strum, Pupillometric Assessment of Small Doses of Opioid in a Pediatric Population p. 20

Elizabeth Malphrus, Characterization of Pediatric Bowel and Bladder Dysfunction via Pupillometry p. 22

Helen C. Miller, PPARGC1A and IGF Polymorphisms Correlate with Greater Strength Performance in Healthy Young Adult Caucasian Cohorts p. 23

Jaisree R. Iyer, Risk Assessment and Management of Children with Congenital Heart Diseases Undergoing Non-Cardiac Surgery p. 25

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Fusion

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Table of Contents:

Kiersten R. Snyder, Optical Coherence Tomography Angiography Imaging of Choriocapillaris in Patients with Age-Related Macular Degeneration p. 26

Leora Aizman, Pushing the Limits: Perinatal Outcomes Beyond Prolonged Second Stage ... p. 27

Marissa Hennelly, Tracheal Aspirate Cultures in Intubated Neonates: A Descriptive Epidemiological Cohort Study p. 29

Puja D. Sheth, Lapse in In-Line Stabilization in Pediatric Trauma Patients p. 30

Sarah Bernstein, Resilience of Children with Chronic Health Conditions: The Impact of Neuropsychiatric Comorbidities p. 31

Siyang Chaili, Consistent Long-Term Therapy of Neovascular AMD Managed by 50 or More Anti-VEGF Injections Using a Treat-Extend- Stop Protocol p. 32

Steven McKenzie, Association of Recently Described RANK and OPG Polymorphisms and Measures of Bone Quality in Young Adults p. 34

Seon Jeong Kim, Cochlear Implantation in a Patient with Early Cochlear Sclerosis due to Sickle Cell Disease p. 35

Thomas D. Zaikos, Class 1-Selective Histone Deacetylase Inhibitors Promote HIV Latency-Reversal and Clearance p. 37

Zachary Zeller, Impact of Polymorphisms in PTK2 on Intrinsic Muscle Strength ... p. 39

MEDICAL EDUCATION

Noah Ravenborg, Developing a Curriculum for Fourth-Year Medical Students Emphasizing Social Justice, Cultural Competency, Cost Consciousness, and Developing Students into Educators p. 40

Liqi Shu, Enriching the Medical Student Radiology Clerkship: Simulating the Radiologist's Experience p. 41

PUBLIC HEALTH

Jeffrey Roberson, Comparison of HCV-Related Diagnoses, Liver Scores, and Mortality in Patients Based on HIV Status Between 2008-2015 at DC-VAMC ... p. 43

Rose Kleiman-Weiner, The Impact of Changing Scope of Practice Laws on Nurse Practitioner Billing Patterns p. 44

S. Laura Chung, How the European Union Is Embracing Cross-Border Telemedicine and What the U.S. State Medical Boards Can Learn From It . p. 46

Saadia Nawal and Cayla Vila, Understanding Nurse, Family, and Interpreter Involvement in Family-Centered Rounds at Children's National Health System p. 49



Janine Amirault, MSII



Sarah McCormack, MSII

From the Editors:

With the goal of highlighting the novel research carried out by the medical students of the George Washington University (GW) School of Medicine and Health Sciences (SMHS), we proudly present the 2018 edition of *Fusion*. This journal is a medical student-run publication; everything from the abstracts to the cover artwork was provided by our peers. This year's collection of abstracts reflects the diverse nature of research being done at SMHS, from research in basic science and clinical medicine to medical education and public health.

Our goal as this year's co-presidents of the William H. Beaumont Medical Research Honor Society was to build upon the tremendous success of last year's journal. We believe that our growing journal reflects an increasing trend of SMHS students' participation in research and an expanding institutional emphasis on research at GW. We also hope that this journal inspires incoming and matriculated medical students to engage in research at GW and become a part of the flourishing SMHS research community.

We would like to offer special congratulations to Nicole Casasanta, Dara Baker, and Christina Pugliese, this year's first-, second-, and third-prize winners, respectively, of the William H. Beaumont Medical Honor Society Student Research Award. Their research stood out among a

truly impressive body of work and merits the opportunity to present the research to faculty and students at the 23rd Annual SMHS Research Day.

This year's edition of *Fusion* would not have been possible without the support of numerous individuals. First, we express our heartfelt gratitude to *Fusion*'s faculty adviser, Alison K. Hall, associate dean for research workforce development. We would also like to thank Laura Radville Wittenbach, research program associate, for her invaluable logistical support. In addition, we thank the SMHS Office of Communications and Marketing for the design and production of *Fusion*. And last, but not least, we offer a special thank you to our fellow classmates — those who volunteered their time to our Editorial Board, as well as our authors, without whom this journal would not exist.

We hope you enjoy the 2018 edition of *Fusion*, a collection of abstracts we believe reflects the unique and impressive research done by GW medical students in a variety of disciplines. To next year's authors and editors: we hope you are inspired by the breadth of research done at GW SMHS, and we encourage you to submit your abstracts and get involved with the 2019 edition of *Fusion* and the William H. Beaumont Medical Honor Society!

Janine Amirault, MSII
Sarah McCormack, MSII

Co-Presidents of the
William H. Beaumont Medical
Research Honor Society



From the Faculty Adviser

I'm delighted to assist the student editors with this edition of *Fusion*. This is an exciting time to be at the George Washington University School of Medicine and Health Sciences, with new initiatives in our research programs that bring greater opportunities for medical student research. You will find examples of the broad range of research pursued by students, from basic biomedical discovery to clinical and translational research with patients to initial translation to practice and communities, on every page of this edition of *Fusion*.

This year, the editors asked authors about their roles in the projects, and medical students described numerous sophisticated approaches and activities including chart review, data collection, molecular biology techniques, field studies, study design, assisting in IRB applications, and statistical analyses, to name a few. I am particularly impressed that so many students reported

findings derived from just one summer of research! It was a real challenge to select the abstract winners from a collection of such excellent projects, and I applaud the hard work shown by all the students and their mentors.

Fusion is just one effort of the William Beaumont Research Honor Society to engage GW medical students in the excitement and impact of research, and I welcome you to explore pp. 4-49 for additional ways to join this community of scholars.



Alison K. Hall, PhD, Associate Dean for Research Workforce Development, Professor of Neurology

RESEARCH SCHOLARLY CONCENTRATION

About 50 students per year elect to join the Clinical and Translational Research Scholarly Concentration. In this program, students conduct mentored research over the summer between MSI and MSII, attend research lectures, and follow-up with research scholarship.

For details, see smhs.gwu.edu/oso/track-program/clinical-and-translational-research



GW RESEARCH FELLOWSHIPS

The GW School of Medicine and Health Sciences offers a variety of competitive scholarship programs to assist in funding exceptional projects in health care and medicine. In 2017, 33 students won a Gill Summer Research Fellowship and 42 students won a Health Services Scholarship. For details, see <https://tinyurl.com/ybu4z3w5>.



Stephanie Kao, MSII, won a 2017 Gill Fellowship to conduct cancer research.

EXTERNAL FELLOWSHIPS

Research track member **Sharjeel Chaudhry**, MSIII, won the Sarnoff Cardiovascular Research Fellowship in 2017 to conduct research at Harvard Medical School. Fellowship opportunities are listed at <https://tinyurl.com/y9vj54gj>.

Savannah Smith, MSII, (right) received a grant from the American College of Rheumatology that funded summer research and travel to its 2017 annual meeting.



METEOR PROGRAM

The Mentored Experience to Expand Opportunities in Research is a competitive fellowship for underrepresented-in-medicine students. Incoming medical students attend two funded summer internships (before matriculation and in the summer between MSI and MSII) and enroll in the research track. For details, see smhs.gwu.edu/academics/md-program/admissions/METEOR

To learn more, please contact the Office of Student Professional Enrichment at www.smhs.gwu.edu/ospe.

TRAVEL AWARDS: Medical students are encouraged to apply for outside funding for summer or year-out research, or for travel to meetings. The Scholarly Concentration website has a list of funding opportunities for summer research, travel, and yearlong fellowships (<https://tinyurl.com/y9vj54gj>).

RESEARCH DAYS AT GW



At Research Days 2017, Sharjeel Chaudhry, Lauren Jacobs, and Brendan Campbell accepted the William Beaumont Research Award from former Fusion editors Michael Froehlich and Jacob Rubin.

GW Research Days is an annual event in the spring that celebrates research across GW. Students and post-doctoral fellows present posters, give oral presentations and compete for cash prizes. For more information, visit researchdays.gwu.edu/.

WILLIAM H. BEAUMONT RESEARCH HONOR SOCIETY



Sarah McCormack, MSII, co-president of the William H. Beaumont Medical Research Honor Society, won first place for medical student posters at the 2017 Research Days.



Justin Buro took a year out in 2017 to conduct research at the Laboratory of Bioregenerative Medicine and Surgery at Weill Cornell Medical College.

YEAR-OUT

Medical students may elect to take a year off from studies at GW to conduct research full-time at GW, NIH, or other institutions. This is a great way to fully immerse yourself in a research project and form connections at other institutions.

RESEARCH PRIZES

Medical students can win prizes for research. The 2018 Doris DeFord Speck and George Speck Endowed Prize will be presented to a student who demonstrates exceptional dedication to biomedical research.

Named after William Beaumont, a pioneer in physiologic investigation, the William H. Beaumont Medical Research Honor Society was established to educate and inform medical students about research. Any GW medical student interested in research is welcome to join. The 2017-18 Co-Presidents are Sarah McCormack and Janine Amirault. See <https://tinyurl.com/y7yuwr6w>.

Relationship Between Hereditary Cancer Syndromes and Oncotype DX Recurrence Score

Nicole Casasanta, MSII, and Sarit Toltzis, MSIV (below)



ADVISER:

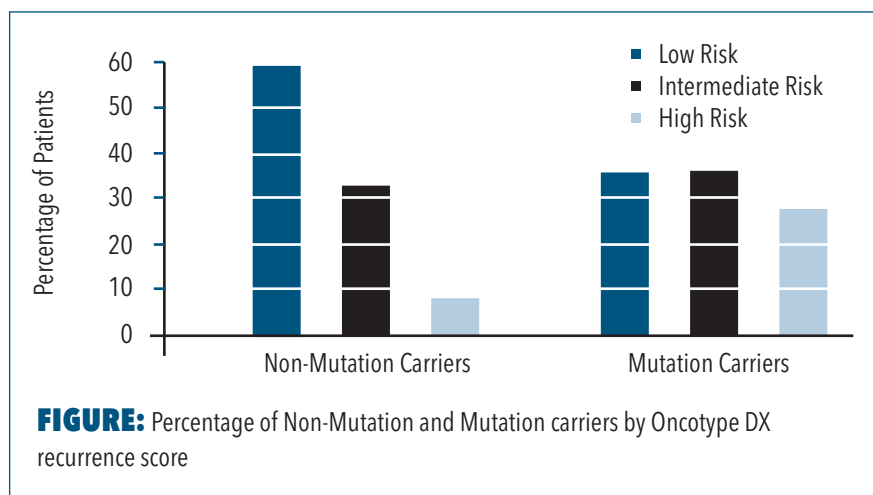
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Oncotype DX is a commercially available test which generates a recurrence score (RS) based on the molecular features of an individual's breast cancer. The RS is used to stratify hormone receptor positive breast tumors into those likely to respond to cytotoxic chemotherapy. Women and men with hereditary cancers tend to have tumors that are chemosensitive.¹ However, studies show that women with known hereditary breast cancer can have a more aggressive clinical course and poor clinical outcomes when compared to sporadic breast tumors. We hypothesize that a high RS may harbor a signal of potential hereditary risk. This analysis aims to identify whether breast cancer patients with hereditary cancer syndromes have a disproportionate amount of high RS compared to sporadic cases.

Individuals with a personal history of breast cancer who received treatment at participating research facilities and had hormone receptor positive breast cancer, Oncotype DX



testing and hereditary cancer mutation testing were included. Oncotype DX RS was recorded along with the type of genetic testing and the genetic testing results. RS was categorized as low (0-17), intermediate (18-30), and high (31+). Those with deleterious mutations in any known hereditary cancer gene were considered positive. Individuals with a variant of uncertain significance (VUS) or negative genetic testing result were considered negative. Difference in distribution of tumors with low, intermediate, and high Oncotype DX results in those with hereditary breast cancers compared to those with sporadic breast cancers was determined with Chi-square and Chi-square difference of proportions.

Data from 1,799 patients with Oncotype DX testing from two clinical sites were collected from 2008. Of those, 499 underwent genetic risk assessment. Mutations were identified in 47 patients and included the following genes: BRCA2 (20); CHEK2 (6); BRIP1 (4); MSH6 (3); PALB2 (3); ATM (3); BRCA1 (2); NBN (2); MUTYH (2); APC (1); MRE11A (1);

P53 (1). Of those testing positive for a deleterious mutation, the number of patients with RS results in each category were 17, 17, and 13 for low, intermediate, and high, respectively. For those considered negative on hereditary cancer panel testing, the RS results were 267, 149, and 36, respectively. Of those with high RS, 28% had deleterious mutations. Chi square test was statistically significant for a difference between the RS of those with deleterious hereditary mutations versus those with sporadic cancers ($p=0.000029$). Chi square test for difference of proportions was also statistically significant for a larger proportion of high RS in mutation carriers ($p=0.0001$). With removal of BRCA2 (20) and BRCA1 (2) carriers from the analysis, the Chi square test for difference of proportions was still statistically significant for a larger proportion of high RS seen in non-BRCA1/2 mutation carriers ($p=0.0069$).

Breast cancer patients with hereditary cancer syndromes have a disproportionate amount of high RS scores compared to sporadic cases.

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Non-BRCA1/2 mutation carriers also had a significantly higher proportion of high RS scores compared to sporadic cancer patients. High RS may indicate a higher likelihood of harboring a hereditary cancer syndrome. This may implicate a high Oncotype DX recurrence score as an independent risk factor for harboring a genetic mutation and thus prompt genetic testing regardless of family history. Further investigation with larger numbers and multivariate analysis is

Recurrence Score	Non-Mutation Carriers (N=452)	Mutation Carriers (n=47)
LOW (%)	267 (59)	17(36)
INTERMEDIATE (%)	149 (33)	17 (36)
HIGH (%)	36 (8)	13 (28)

TABLE: Influence of hereditary cancer mutations on Oncotype DX recurrence score in breast cancer patients

needed to validate if a high RS serves as an independent predictor of benefit

versus sporadic breast cancers: Differences based on germline mutation status. Cancer. 2016; 122(8), 1178-1184.

from genetic counseling and testing.

REFERENCES

1. Narod SA, Metcalfe K, Lynch HT, et al. Should all BRCA1 mutation carriers with stage I breast cancer receive chemotherapy? Breast Cancer Res Treat. 2013;138: 273-279.

2. Shah SA, Patil S, Dickler MN, et al. Twenty-one-gene recurrence score assay in BRCA-associated

The Role of DFMO in Helicobacter Pylori Infection: Modulation of ROS Response

Dara Baker,
MSII

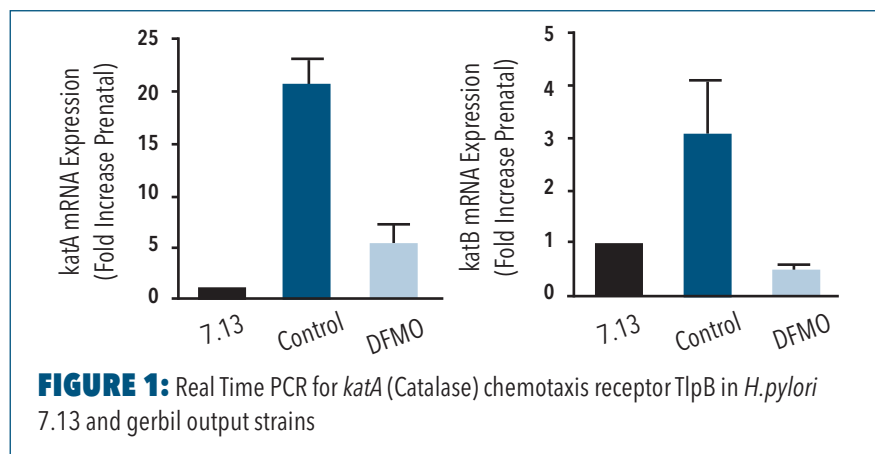
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Gastric cancer remains the third foremost cause of cancer deaths worldwide. The leading cause of gastric cancer, *Helicobacter pylori*, is thought to drive carcinogenesis by inducing chronic inflammation. One pathway implicated in the host immune response involves polyamines, which have been shown by our laboratory to contribute to gastric carcinogenesis.^{1,2}

Difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase (ODC), the rate-limiting enzyme for polyamine synthesis, reduces gastric inflammation and progression to cancer in gerbils infected with *H. pylori*.³ Paradoxically,



cell-specific deletion of the *Odc* gene in macrophages increased inflammation in murine experiments, indicating the likely involvement of alternative mechanisms by which DFMO could be mediating cancer progression, including direct effects on the bacteria.^{4,5} We hypothesize that DFMO modulates the interaction between *H. pylori* and gastric cancer by affecting the bacteria exposed to oxidative stress generated in an inflammatory environment.

Strains for *H. pylori*, derived from the parental strain 7.13, were either

grown on plates passaged 19 times with or without DFMO exposure, or harvested from gerbil stomach tissue after 12 weeks with or without exposure to DFMO in drinking water. Murine macrophages of the RAW 264.7 cell line and *H. pylori* strains were co-cultured, and mRNA was harvested from cells six hours post-infection. RT-PCR was used to analyze expression of genes encoding proteins indicative of M1 macrophage activation response (NOS2, TNF- α ,

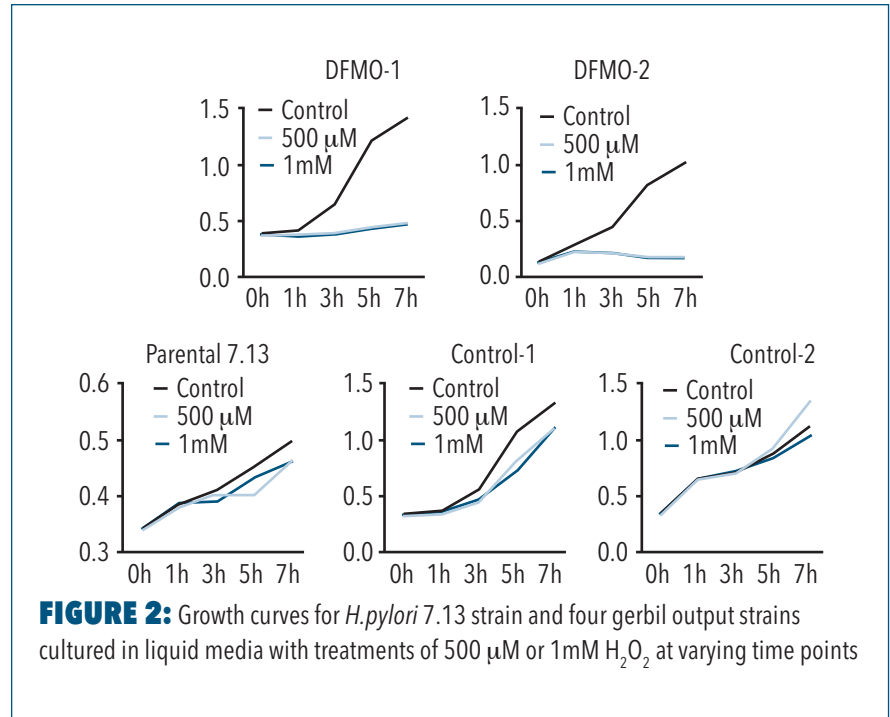
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IL-1®). For the second focus, we cultured *H. pylori* 7.13 in liquid media over 24 hours with 50 mM DFMO, 50 mM ornithine, or no additional reagent. At each two-hour time point, we noted the OD_{600nm} and isolated RNA. To assess oxidative response, we used RT-PCR to compare mRNA expression of genes involved in *H. pylori* defense mechanisms to ROS/RNS, including *sodB* and *tpx*. We performed RT-PCR for *katA* and *tlpB* for the parental, in vitro passaged, and gerbil output strains. Last, we grew the parental strain and 4 gerbil output strains in Brucella broth, or broth treated H₂O₂, and plotted growth curves.

In co-culture experiments, M1 gene expression levels did not differ between macrophages infected with DFMO-treated or control strains. In our analysis of *H. pylori* gene expression, we found *sodB* and *tpx* genes to be induced at the two and four hour time points in the samples collected from the DFMO-treated compared to ornithine-treated media or untreated controls. Furthermore, expression of *katA* and *tlpB* were lower in DFMO output versus control output strains (Figure 1). Bacterial growth curves demonstrated attenuated growth in H₂O₂-treated DFMO-exposed *H. pylori* strains compared to untreated DFMO-exposed controls (Figure 2). Additionally, unexposed control gerbil output strains showed no difference in growth in acutely H₂O₂-treated strains compared to untreated controls.

Our results from this study suggest that chronic exposure of *H. pylori* to DFMO impedes bacterial response to environmental stress by affecting expression of oxidative defense genes. These data also imply that treatment



with DFMO may be contributing to environmental oxidative stress, which leads to an immediate response by the bacteria to prevent ROS-induced DNA damage. Further studies may establish the specific role of DFMO in the modulation of *H. pylori* growth that hinders the clinical progression of ulcerative disease through induction of oxidative stress. The implications are that DFMO has benefits in its effects on *H. pylori* that add to its chemopreventive potential in patients afflicted with chronic gastritis.

REFERENCES

1. Chaturvedi R, Asim M, Hoge S, Lewis ND, Singh K, Barry DP, de Sablet T, Piazzuelo MB, Sarvaria AR, Cheng Y, Closs EI, Casero RA, Jr., Gobert AP, Wilson KT. Polyamines impair immunity to *Helicobacter pylori* by inhibiting L-arginine uptake required for nitric oxide production. *Gastroenterology*. 2010;139: 1686-98. PMID: PMC2967614.
2. Chaturvedi R, de Sablet T, Asim M, Piazzuelo MB, Barry DP, Verriere TG, Sierra JC, Hardbower DM, Delgado AG, Schneider BG, Israel DA, Romero-Gallo J, Nagy TA, Morgan DR, Murray-Stewart T, Bravo LE, Peek RM, Jr., Fox JG, Woster PM, Casero RA, Jr., Correa P, Wilson KT.

Increased *Helicobacter pylori*-associated gastric cancer risk in the Andean region of Colombia is mediated by spermine oxidase. *Oncogene*. 2015;34: 3429-40. PMID: PMC4345146.

3. Barry DP, Asim M, Leiman DA, de Sablet T, Singh K, Casero RA, Chaturvedi R, Wilson KT. Difluoromethylornithine is a novel inhibitor of *Helicobacter pylori* growth, CagA translocation, and interleukin-8 Induction. *PLoS One*. 2011;6: e17510. PMID: PMC3046249.
4. Hardbower DM, Asim M, Luis PB, Singh K, Barry DP, Yang C, Steeves MA, Cleveland JL, Schneider C, Piazzuelo MB, Gobert AP, Wilson KT. Ornithine decarboxylase regulates M1 macrophage activation and mucosal inflammation via histone modifications. *Proc Natl Acad Sci USA*. 2017;114: E751-E60. PMID: PMC5293075.
5. Gobert AP and Wilson KT. NADPH-dependent generation of ROS during *Helicobacter pylori* infection: a blessing in disguise. *Free Radical Biology and Medicine*. 2017;105: 16-27.

Etiology and Management of Hospitalized and Outpatient Diarrhea Among Children Less Than 5 Years of Age in Lambaréné, Gabon

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Diarrhea remains the second leading cause of death among children ages 1–59 months, with nearly half of deaths occurring in Sub-Saharan Africa.¹ World Health Organization (WHO) guidelines on the management of childhood diarrhea recommend oral rehydration salts (ORS), continued feeding or breastfeeding, and zinc supplementation for all children with diarrhea to prevent dehydration and malnutrition; antibiotics only for bloody diarrhea (i.e. probable shigellosis), suspected cholera, or severe non-intestinal infections (e.g. pneumonia or sepsis); and avoidance of anti-diarrheal drugs and antiemetics for acute or persistent diarrhea.²

		N = 45	
Gender	Female	26 (58%)	
	Male	19 (42%)	
Age	0–11 mos	20 (44%)	
	12–23 mos	17 (38%)	
	24–59 mos	8 (18%)	
Mean time since onset of diarrhea before presentation to hospital		4.7 [1, 21] days	
Mean number of stools in last 24 hr		4.1 [1,9]	
Macroscopic blood in stool		8 (18%)	
Mucous in stool		30 (67%)	
Fever (body temperature ≥ 38°C)		34 (76%)	
Vomiting		17 (38%)	
Extra-intestinal		27 (60%) [25 pulmonary signs, including 16 cough, 5 bronchitis, 4 rhinitis; 1 anemia; 1 dermatologic sign]	
Malaria (positive smear)		3 (7%)	
Measles		2 (4%)	
Nutritional Status	Severe malnutrition	31 (79%)	
	Moderate malnutrition	4 (10%)	
Diet	Children < 6 mos	Current breastfeeding	7 (88%)
		Never breastfeed	1 (12%)
	Children ≥6 mos	Breastfed ≥ 6 mos	20 (61%)
		Breastfed < 6 mos	10 (30%)
		Never breastfed	3 (9%)

TABLE: Clinical and demographic characteristics of cases

Gabon is an upper-middle income country in Sub-Saharan Africa for which there is a lack of recent high quality data on the etiology and management of childhood diarrhea.³ This prospective study aimed to describe the etiology, clinical symptoms, associated demographic factors, and

management of hospitalized and outpatient cases of diarrhea in Gabonese children under 5 years of age.

Children ≤ 59 months presenting to the Albert Schweitzer or George Rawiri Regional Hospitals in

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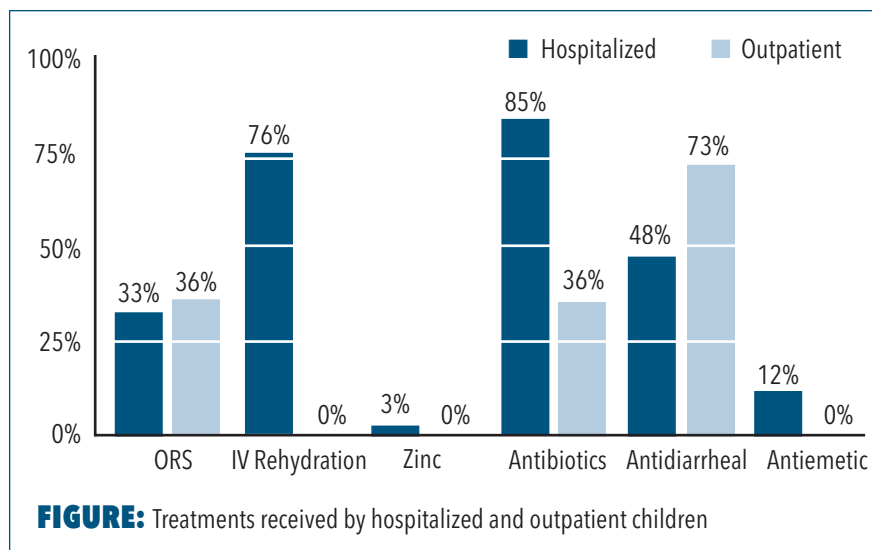
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Lambaréné, Gabon (February–July 2017) were included if they had ≥ 3 liquid stools per day within the past three days. Both outpatient and hospitalized cases were included. Dehydration and nutritional status were defined according to WHO standards.² Diarrheaogenic *Escherichia coli*, *Salmonella enterica*, and *Shigella* spp. were detected using conventional culture techniques. Samples were tested for rotavirus, adenovirus, and *Cryptosporidium* spp. antigens using commercial rapid immunoassays. Multiplex PCR was used to detect *Cryptosporidium* spp., *Giardia intestinalis*, and *Cyclospora cayetanensis* on extracted DNA from feces.

Forty five children were included in the study, 34 of whom were hospitalized. Clinical and demographic characteristics are described in Table 1. Prescribed treatments are summarized in Figure 1. Forty-nine percent of children were infected with one or more of the above sought-for pathogens, most commonly with *Giardia intestinalis* (28.9%) or *Cryptosporidium* spp. (24.4%).

This study highlights the management of childhood diarrhea in Lambaréné, Gabon, in the context of WHO guidelines. Only 33% and 36% of hospitalized and outpatient children, respectively, received ORS. Zinc was given to only one (3%) hospitalized patient and was never prescribed in the outpatient setting. Moreover, despite potentially harmful side effects in pediatric patients and their lack of benefit, antidiarrheal drugs were frequently given to both hospitalized (48%) and outpatient (73%) children.

Antibiotics were prescribed in 85% and 36% of hospitalized and outpatient cases, respectively, while



only eight children (18%) presented with macroscopic blood in the stool. This observed overuse of antibiotics is consistent with previous studies and is concerning given reports of high levels of antimicrobial resistance in Sub-Saharan Africa.⁵

Previous studies have shown that acute malnutrition is a risk factor for severe diarrhea and death during hospitalization.⁴ Seventy nine percent of children presented with severe acute malnutrition and an additional 10% with moderate acute malnutrition. To prevent malnutrition, WHO recommends exclusive breastfeeding for the first six months of life.² While 61% of children ≥ 6 months had been breastfed for at least the first six months of life, 21% of all children had never been breastfed.

This study emphasizes the need for continued education of healthcare workers and communities regarding WHO recommended treatment of childhood diarrhea. This includes ORS, zinc supplementation, and continued feeding or breastfeeding to prevent dehydration and malnutrition; avoidance of antidiarrheal drugs; and restricted use of antibiotics to limit the spread of antimicrobial resistance.

REFERENCES

1. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: An updated systematic analysis with implications for the Sustainable Development Goals. *The Lancet*. 2016;388(10063): 3027–3035.
2. The treatment of diarrhoea — A manual for physicians and other senior health workers. World Health Organization, 2005. (Accessed July 10, 2017, at http://www.who.int/maternal_child_adolescent/documents/9241593180/en/)
3. Stratégie de coopération de l’OMS avec le Gabon 2016–2021. Organisation mondiale de la santé (OMS), 2017. (Accessed July 10, 2017, at <http://apps.who.int/iris/bitstream/10665/254892/1/ccs-gab-2016-2021-fr.pdf?ua=1>.)
4. Breurec S, Vanel N, Bata P, Chartier L, Farra A, Favennec L, et al. Etiology and epidemiology of diarrhea in hospitalized children from low income country: a matched case-control study in Central African Republic. *PLOS Neglected Tropical Diseases*. 2016;10(1):e0004283.
5. Swierczewski BE, Odundo EA, Koech MC, Ndonye JN, Kirera RK, Odhiambo CP, et al. Surveillance for enteric pathogens in a case-control study of acute diarrhea in Western Kenya. *Trans R Soc Trop Med Hyg*. 2013;107(2):83–90.

Alterations to Maternal Cortical and Trabecular Bone in Multiparous Middle-Aged Mice

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During the reproductive cycle, altered calcium homeostasis is observed due to variable demand for mineral requirements. This results in increased bone resorption during the time period leading up to parturition and subsequent lactation. During lactation, women will lose 1-3% of bone mineral density per month, which is comparable to the loss experienced annually post-menopausal.¹ The purpose of this study was to determine the effect of parity on bone formation in middle-aged mice.

C57BL/6J mice were obtained and breeding pairs were established to obtain timed pregnancies. Females were retired from breeding when litter size decreased, which was approximately at 9 to 12 months of age, and then enrolled in the current study. Mice were then euthanized and the right distal femurs were analyzed by standard micro-computed tomography. For each femur, the trabecular bone compartment was sliced into 50 segments from the cortical shell

Number of Litters	Number of mice	avg age (days)	avg litter size (pups. litter)	avg time to first litter (days)	avg time to last litter (days)
1	6	283±27	6.5±3.5	137±0	137±0
2	5	295±22	7.8±1.3	114±34	155±35
3	29	218±23	7.6±2.0	94±29	219±44
4	13	339±31	6.3±1.3	89±22	272±39
5	2	355±35	8.0±0.3	74±6	283±24

*avg = average

TABLE: Number of total litters, average age, mice per litter, age at birth of first litter, and age at birth of last litter

in a region approximately 0.5 mm above the most proximal portion of the growth plate. From the images, the following three-dimensional bone volume parameters were calculated: trabecular bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N) and trabecular separation (Tb.Sp). The trabecular bone compartment and the cortical bone sections were assessed. Following data extraction, linear regressions using ANOVA with Tukey's test were performed to compare groups.

In this study, 63 female mice were used. The number of mice in each group, age, mice delivered in each litter, and time between litters were tracked for all mice and subsequently analyzed and recorded (Table). BV/TV had decreased as pregnancies increased from one to five litters (Figure). Interestingly, mice with no pregnancies had a smaller trabecular bone BV/TV than mice with one pregnancy (Figure). All groups showed statistically significant differences from the mice with one litter ($p < 0.05$). Trabecular number decreased as

number of litters increased (from one to five litters). Mice that had one litter had significantly higher Tb.N than other groups, including mice with no pregnancies. Analysis of trabecular thickness and spacing revealed no significant difference with respect to number of pregnancies. With respect to cortical bone analysis, no differences were found in BV/TV or in cortical bone area. No differences were observed in cortical bone porosity.

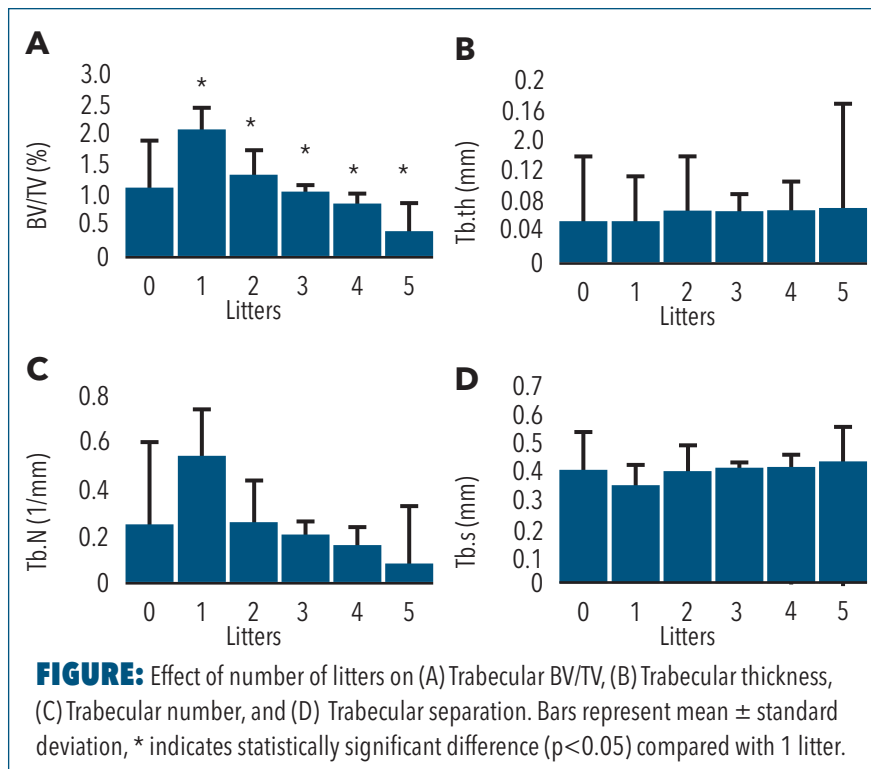
When analyzing the trabecular bone of mice in this study, a correlation was observed between parity and bone density. As the number of litters increased (from one to five litters), measurements of trabecular bone in BV/TV and Tb.N both decreased. These results may suggest that more trabecular bone is broken down as number of pregnancies increases. However, while Tb.N decreased, there was no correlation seen in the width or spacing of the rods and plates that make up trabecular bone. There were also no significant differences in tissue mineral density or cortical

Continued on p. 12

bone parameters. Taken together, these data sets suggest that parity in mice affects trabecular bone, but does not impact cortical bone or the total density of the bone. Furthermore, it seems increasingly likely that there are additional compensatory mechanisms at play to preserve bone health. These observations are supportive of a previous claim of the presence of cortical bone compensation in multiparous mice to offset an increased risk of postmenopausal bone fracture.² However, additional studies are required in order to further elucidate the presence of cortical bone compensation.

REFERENCES

1. Kirby BJ, Ardeshipour L, Woodrow JP, Wysolmerski JJ, Sims NA, Karaplis AC, et al. Skeletal recovery after weaning does not require PTHrP. *J Bone Miner Res.* 2011;26:1242-51.



2. MJ de Bakker C, Altman-Singles AR, Li Y, Tseng W, Li C, Liu XS. Adaptations in the Micro-architecture and Load Distribution of

Maternal Cortical and Trabecular Bone in Response to Multiple Reproductive Cycles in Rats. *J Bone Miner Res.* 2017.

Secretomic Analysis of Spent Embryo Culture Media

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	Well 1	Well 2	Well 3
Outcomes of embryos	46,XY 46,XX Two embryos arrested	Three embryos arrested	46,XX Blastocyst with non-concurrent CCS result Two embryos arrested
Media used for analysis	Day 3 media	Not analyzed	Day 5 media

TABLE 1: Embryo Culture media droplets

Preimplantation genetic screening (PGS) with euploid blastocyst transfer has facilitated the selection of embryos most suitable for replacement and the optimization of IVF outcomes.¹ Non-invasive determinants of embryonic competence

could be used independently or in conjunction with pre-implantation genetic screening (PGS) for embryo selection.^{2,3} Promising methods for evaluating embryonic implantation potential include the evaluation of substrates or byproducts of embryo

metabolism, such as metabolite utilization and the assessment of secreted proteins or metabolites in spent embryo culture media (secretome).^{4,5} Using tandem mass spectrometry

Continued on p. 13

(MS), we sought to investigate the embryonic secretome in spent embryo culture media in relation to embryo development and quality. After validation of the technique, the embryonic secretome in relation to aneuploidy and in vitro fertilization (IVF) outcomes will be investigated through a prospective cohort study.

Patients undergoing IVF with comprehensive chromosome screening (CCS) at Shady Grove Fertility Center were eligible to participate. From fertilization until Day 3 of development, embryos were cultured in Continuous Single Culture Medium (Irvine Scientific) supplemented with Serum Protein Substitute (Origio). From Day 3 of development until the blastocyst stage (Day 5 or 6), embryos were cultured in Blastocyst Medium supplemented with human serum albumin (Origio). Embryos were co-cultured in groups of three or four from fertilization until the blastocyst stage was obtained (Table 1). An immunoaffinity depletion strategy was used to deplete high abundant serum proteins (i.e. albumin) from media samples. The remaining proteins secreted into the media were digested with trypsin using pressure cycling technology and peptide digests were analyzed by nanoflow liquid chromatography (LC) coupled with a high-resolution Orbitrap Fusion Lumos mass spectrometer. Tandem mass spectra were searched against a SwissProt human protein database and the relative

	Well 1, Day 3 Sample	Well 1, Day 3 Control	Well 3, Day 5 Sample	Well 3, Day 5 Control
Total PSMs	1,701	787	1,101	1,796
Total Proteins	273	195	133	230
Proteins 2+ PSMs	158	90	76	125
Albumin (PSM)	24	16	3	15

TABLE 2: Albumin composition of analyzed media samples

abundance of proteins were determined by comparing the number of peptides identified per protein across all samples (spectral counting).

Albumin and high abundant proteins were successfully depleted from the embryo culture media, as evidenced by the low peptide-to-spectrum matches (PSM) of albumin after the Multiple Affinity Removal System protocol. There were no significant differences in the secretome of spent embryo culture media between control samples and those in which embryos were cultured (Table 2). This may be a limitation related to depletion of albumin and associated bound proteins.

The use of a Multiple Affinity Removal System protocol resulted in successful depletion of albumin and high abundant proteins in embryo culture media, which may facilitate the detection of low abundance proteins. After albumin depletion, no differences in the secretome between control and sample embryo culture media droplets were detected. Further validation studies are underway to refine the technique and subsequently move

forward with this pivotal clinical trial.

REFERENCES

1. Scott RT, Upham KM, Forman EJ, Hong KH, Scott KL, Taylor D, et al. Blastocyst biopsy with comprehensive chromosome screening and fresh embryo transfer significantly increases in vitro fertilization implantation and delivery rates: a randomized controlled trial. *Fertil Steril.* 2013;100:697-703.
2. Gardner DK, Wale PL. Analysis of metabolism to select viable human embryos for transfer. *Fertil Steril.* 2013;99:1062-72.
3. Katz-Jaffe MG, McReynolds S. Embryology in the era of proteomics. *Fertil Steril.* 2013;99:1073-7.
4. Katz-Jaffe MG, Schoolcraft WB, Gardner DK. Analysis of protein expression (secretome) by human and mouse preimplantation embryos. *Fertil Steril.* 2006;86:678-85.
5. Lawlor K, Nazarian A, Lacomis L, Tempst P, Villanueva J. Pathway-based biomarker search by high-throughput proteomics profiling of secretomes. *J Proteome Res.* 2009;8:1489-503.

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Efficacy of Manipulation Under Anesthesia for Stiffness Following Total Knee Arthroplasty: A Systematic Review

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Knee stiffness following primary total knee arthroplasty (TKA) can lead to unsatisfactory patient outcomes, including failure to meet the target functional outcomes for the procedure.^{1,2} Stiffness is characterized by limited range of motion (ROM), frequently associated with pain and knee dysfunction. Manipulation under anesthesia (MUA) remains a viable option for treatment of post-operative stiffness. However, the efficacy and optimal timing of manipulation of anesthesia remains unknown.

A systematic review of the literature was performed to identify studies that reported clinical outcomes for patients who underwent MUA for post-operative stiffness treatment. The search resulted in 727 abstracts that were examined to determine the efficacy of MUA for stiffness post-TKA. Following elimination of duplicate articles, predetermined inclusion and exclusion criteria were applied. In total, 24 articles met the inclusion criteria. Of these 24 articles, three papers were excluded due to incomplete data.

Twenty one studies reported data on primary MUA outcomes in over 1,300 total patients (Table 1). The mean sample patient population size was 82.6 per study (range: 21–195).

Study	Patient count	Number of Knees	Incidence of MUAs in TKA Population	Motion pre-TKA	ROM pre-MUA	Time between TKA & MUA	ROM at final follow-up	Gain in motion	Significant Improvement in final ROM or flexion?	Time between MUA and last reported data	Complications
Desai	86	--	0.023	---	53.3	22w	76.7	23.3	Yes	12m	1
Ipach	39	--	0.045	104.9*	67.96*	10.81w	94.5*	26.54*	---	1.5m	1
Yoo	16	22	0.005	102.5	64.5	4.7w	113.4	48.9	---	64.3m	--
Dzaja	72	--	0.012	---	69.8	9w	---	---	---	37.7m	0
Ferrel	161	177	---	---	85.64	---	111.7	26.06	Yes	19.3m	0
Choi	143	149	---	---	61.44	8.6w	100.7	39.26	Yes	23.4m	0
Issa*	134	145	0.07	101	81	5.5w	114	33	Yes	51m	1
Issa**	169	169	---	---	---	---	112.45	---	---	53.05m	---
Keating	90	113	0.018	102*	70*	10w	105*	35*	Yes	60m	1
Mohammed	21	21	0.04	---	60.2	13.2w	90.4	30.2	Yes	3.02m	0
Cates	37	37	0.06	111	78	---	104	26	---	12m	0
Rubinstein	33	36	0.046	109	73	---	113	40	Yes	46m	1
Yercan	46	---	0.0387	---	67	5.6w	114	47	Yes	31m	0
Maloney	---	24	0.112	---	67	7.3w	111	44	No	---	---
Esler	42	47	0.088	102*	62*	11.3w	95.6*	33.6*	Yes	12m	0
Fox	---	76	0.23	96*	71*	2w	101*	30*	---	12m	5
Yeoh	48	48	0.023	93*	53*	12.3w	86*	33*	Yes	90m	0
Namba	195	195	0.02	---	74*	15.5w	98.8*	24.8*	Yes	9.93m	0
Daluga	60	94	0.12	107*	61*	---	103*	42*	---	34.8m	1
Bawa	96	119	0.0369	96.5	64.7	10.6w	99.2	34	Yes	37.2m	0

*Indicates value present is flexion rather than ROM in table 1

TABLE 1: Summation of Measured Variables by Study

Based on available data from 17 papers, the mean prevalence of patients that underwent MUA after TKA was 5.8% (Table 1). The time between TKA and MUA was provided in 15 studies and ranged from two weeks to 22 weeks with an aggregate mean of 9.9 weeks (Table 1). The mean pre-TKA motion and/or flexion was greater than 100 degrees in all reporting studies except Fox et al., Bawa et al., and Yeoh et al., who reported populations that had a pre-TKA flexion of 96, 96.5, and 93 degrees, respectively (Table 1). Post-MUA, a mean ROM of greater than 90 degrees at final follow up was achieved in all studies except two (Table 1). The time at which final ROM measurements were recorded varied from six weeks to seven and a half years, with a mean

follow-up time of 32 months across all reporting studies (Table 2; Table 1). There was significant improvement in flexion or total range of motion post-MUA versus pre-MUA in all reported studies ($p < 0.05$) (Table 1). Several studies commented on the effect of latency between TKA and primary MUA on outcomes. The most common time point used to evaluate this outcome was approximately three months (Table 2). Six of the 21 studies reported a complication associated with the primary MUA procedure, yielding a complication rate of less than 1% (Table 1).

MUA remains an efficacious, low-risk, and minimally invasive treatment option for post-operative stiffness following TKA. Compared

Continued on p. 15

to before MUA, our study found a mean overall gain in flexion of 32.1 degrees and an overall gain of 35.8 degrees of ROM after MUA (Table 1). Based on the included data comparing cohorts undergoing MUA at various time points, our study indicates that MUA should be performed between four and 12 weeks (Table 2). Without significant evidence of greater benefit before four weeks, conservative management of stiffness warrants an adequate trial. Four to 12 weeks is an optimal time for intervention because it balances the need to attempt conservative management with the greater effect size for improved flexion/ROM after MUA within this period. In summary, MUA provides clinically significant improvement in ROM for most patients, with the best outcomes occurring in patients treated during the four to 12 weeks post-TKA period.

REFERENCES

1. Kim J, Nelson CL, Lotke PA. Stiffness after total knee arthroplasty: Prevalence of the complication and outcomes of revision. *Journal of Bone and Joint Surgery*. 2004;86:1479-1484.

Study	Timepoint(s) in Question	Pt #	p-value	Finding
Yercan et al.	3w	46	0.021	ROM at final follow-up was greater in cohort before timepoint versus cohort after timepoint
Ipach et al.	30d	39	0.655	No difference in absolute flexion when comparing cohort before timepoint to cohort after timepoint
	30d		0.328	No difference in gain of flexion when comparing cohort before timepoint to cohort after timepoint
Cates et al.	8w	37	0.017	Significantly more flexion gained immediately post-MUA in cohort before timepoint than in cohort after timepoint
			0.203	No difference in gain of flexion at 1-year follow-up when comparing cohort before timepoint to cohort after timepoint
			0.516	No significant difference between cohort before versus cohort after timepoint in extension gained immediately post-MUA
			0.381	No significant difference between cohort before versus cohort after timepoint in extension gained at one-year follow-up
Choi et al.	12w	143	0.24	No difference in achieving 90 degrees of flexion when comparing cohort before timepoint to cohort after timepoint
Keating et al.	12w	90	<0.36	No difference in motion when comparing cohort before timepoint to cohort after timepoint
Yeoh et al.	12w	48	0.3	No difference in range of motion immediately post-MUA when comparing cohort before timepoint to cohort after timepoint
			0.25	No difference in range of motion one-year post-MUA when comparing cohort before timepoint to cohort after timepoint
Daluga et al.	0-21d & 90d	60	0.08	No difference in flexion gain when comparing cohort before timepoint to cohort after timepoint
Namba et al.	90d	195	<0.001	Significant gain in flexion when comparing pre-MUA value to post-MUA value in cohort before timepoint and after timepoint
			0.001	Significant gain in extension when comparing post-MUA to pre-MUA values in before timepoint cohort
			0.057	No significant gain in extension when comparing post-MUA to pre-MUA values in after timepoint cohort
Esler et al.	4m	42	<0.01	Sustained gains in post-MUA flexion compared to pre-MUA flexion in both before timepoint and after timepoint cohorts
Desai et al.	20w	86	0.003	Higher flexion gain at 1 year in cohort before time point compared to cohort after timepoint
	12-14w		0.05	Mean flexion gain when MUA performed between 12-14 weeks post-TKA is greater than MUAs performed later
Bawa et al.	0-45d	---	<0.001	Significantly improved post- MUA flexion compared to pre-MUA values
	46-60d	---	<0.001	Significantly improved post- MUA flexion compared to pre-MUA values
	61-75d	---	<0.001	Significantly improved post- MUA flexion compared to pre-MUA values
	61-75d	---	0.05	Significantly increased final ROM and post-MUA gain when comparing this timepoint to 76-90d timepoint
	76-90d	---	<0.001	Significantly improved post- MUA flexion compared to pre-MUA values
Issa et al.	>90d	---	<0.001	Significantly improved post- MUA flexion compared to pre-MUA values
	0-6w	38*	0.001	Significantly improved post-MUA flexion compared to pre-MUA values
	7-12w	74*	0.001	Significantly improved post-MUA flexion compared to pre-MUA values
	13-26w	17*	0.005	Significantly improved post-MUA flexion compared to pre-MUA values
	>26w	15*	0.01	Significantly improved post-MUA flexion compared to pre-MUA values

TABLE 2: Timing's effect on Primary MUA Motion Outcomes

2. Diduch DR, Scuderi GR, Scott WN, Insall JN, Kelly MA. The efficacy of arthroscopy following total knee replacement. *Arthroscopy: The Journal of Arthroscopic and Related Surgery*. 1997;13(2):166-171.

Efficacy of Outpatient Ketamine Infusions on Different Etiologies of Chronic Pain

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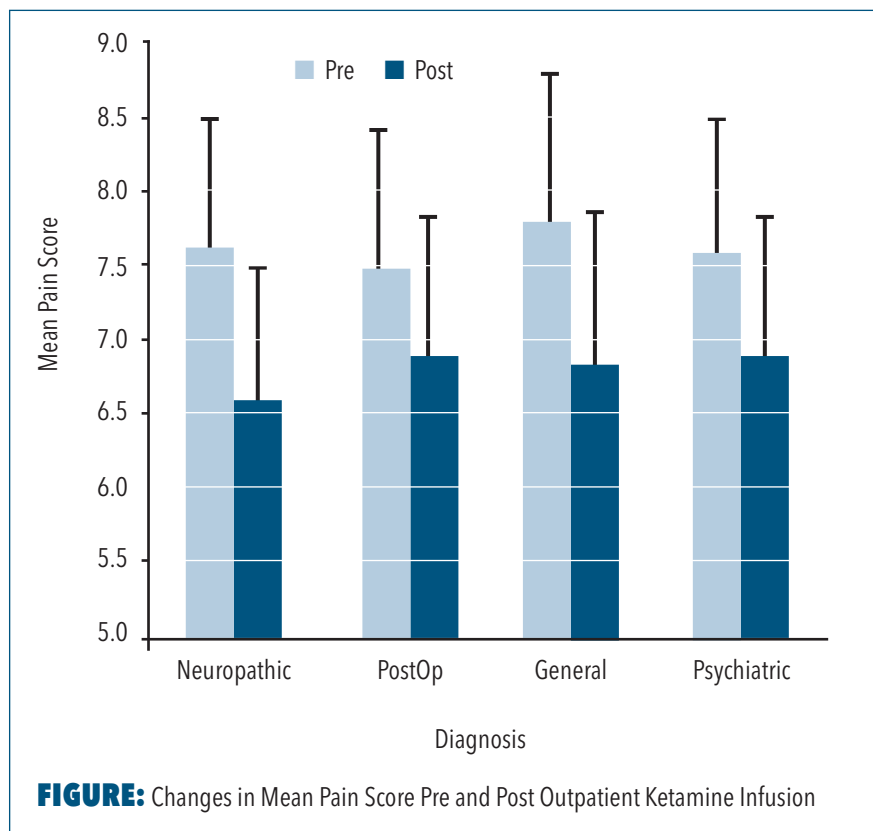


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Ketamine, an NMDA (N-methyl-D-aspartate) antagonist, has been shown to be an effective treatment option for pain management.¹ Previous studies have shown improvement in outcomes in chronic pain patients following ketamine infusions.^{2,3} Chronic pain is determined in a temporal fashion, with an arbitrary timeframe of three to six months, and may be subdivided into nociceptive, inflammatory, neuropathic and dysfunctional categories of pain. In our previous study patients with chronic pain, unresponsive to conventional treatment, demonstrated improved outcomes with outpatient ketamine infusions.⁴ The purpose of this study is to examine the efficacy of outpatient ketamine infusions in patients with various chronic pain conditions.

After IRB approval we examined data on patients undergoing outpatient ketamine infusions. We subdivided patients based on their chronic pain diagnosis into four nonexclusive categories: neuropathic pain, generalized pain, chronic postoperative pain, and chronic pain in patients with a psychiatric diagnosis. Patients



completed the Brief Pain Inventory (BPI) prior to one-day or three-day outpatient ketamine infusions and again two to four weeks after the infusions. We measured pain scores and outcomes related to general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

For data analysis, a random effects mixed model was used to test the time effect (pre versus post) for pain and other outcomes, as well as the diagnosis by time interaction. This method accounted for within-subject autocorrelation of the pain scores.

There were 224 patients in the sample: 143 patients with neuropathic pain (64%), 49 with generalized pain (22%), 80 with chronic post-op pain

(36%), and 63 with psychiatric diagnoses in addition to chronic pain (28%). There was a significant drop in mean pain level from pre- to post-infusion ($p < 0.0001$) for all diagnoses, with the mean pain level dropping from 7.6 (95% confidence interval 6.8 to 8.5) to 6.8 (95% ci 6.0 to 7.7) after adjusting for covariates. The decreases in pain relief among the different groups were not significantly different (Figure).

General activity significantly improved in patients with chronic post-op pain ($p = 0.0062$) and in those with psychiatric diagnosis ($p = 0.0044$). Walking improved significantly in those without chronic post-op pain ($p = 0.025$). Work impairment was significantly less in those with

Continued on p. 17

Continued from p. 16

neuropathic pain ($p=0.01$) and in those without psychiatric diagnosis ($p=0.44$). Sleep impairment was significantly less in those without chronic post-op pain ($p=0.16$).

Outpatient ketamine infusions significantly improved pain scores in patients with the following chronic pain conditions: neuropathic, generalized, chronic post-op pain, and chronic pain in patients with psychiatric

diagnosis. Closer analysis shows that improvement in various quality of life measures differed significantly among different chronic pain conditions.

Further study with larger sample groups may help elucidate ketamine's broad therapeutic effect as interest in this drug's potential for therapy of a multitude of chronic pain conditions increases.

REFERENCES

1. Visser E, Schug SA. The role of ketamine in pain management. *Biomedicine &*

Pharmacotherapy. 2006;60(7):341-8.

2. Schwartzmann RF, et al. Outpatient ketamine infusions for the treatment of complex regional pain syndrome: a double blind placebo controlled study. *Pain*. 2009;147(1-3):107-15.
3. Sigtermans MJ, et al. Ketamine produces effective and long-term relief in patients with CRPS. *Pain*. 2009;145(3):304-11.
4. Kherbach K, et al. Outcome measurements in chronic pain patients receiving patient ketamine infusions. Presentation at IARS Annual Meeting May 2017, Washington, D.C.

A Phase II Study of Copper-Depletion Using Tetrathiomolybdate in Patients with Breast Cancer at High Risk for Recurrence: Updated Results

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Metals have emerged as a viable therapeutic target for a new generation of anti-cancer and anti-metastatic agents. Copper, an essential trace element, serves as an important catalytic cofactor in several biological functions and has emerged as an essential factor in carcinogenesis.¹ It is well established in preclinical mouse models of breast cancer progression that the pre-metastatic niche depends on bone marrow (BM) derived VEGFR2+ endothelial progenitor cells (EPCs) and copper-dependent lysyl oxidase (LOX), among other elements, to create a hospitable microenvironment that supports tumor progression.^{2,3} Prior clinical trials have shown the

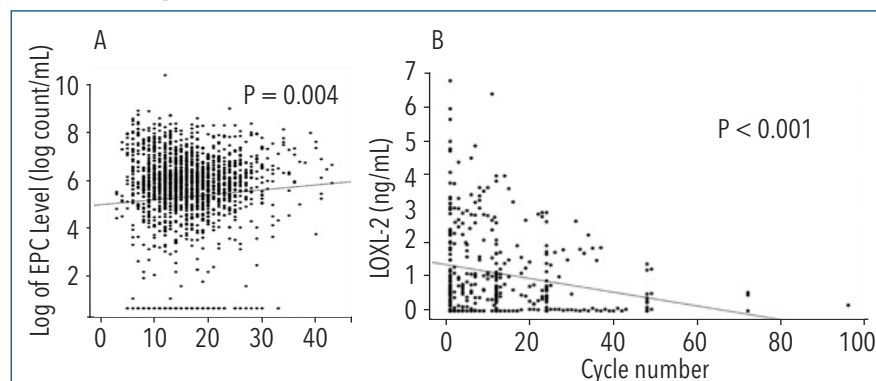


FIGURE: Effect of tetrathiomolybdate on patients at a high risk for recurrence.

A) Reduction in VEGFR2+ EPCs using a mixed-effects model ($P=0.004$); B) Lysyl oxidase 2 (LOXL-2) were markedly reduced at 12 and 24 months ($P<0.001$). Both VEGFR2+ EPCs and LOX condition the pre-metastatic niche and create a permissive environment for tumor metastases.

efficacy of tetrathiomolybdate (TM), an oral copper chelator, to reduce serum ceruloplasmin (Cp) levels while being safe and well-tolerated in advanced cancer patients.⁴ We hypothesized that TM-associated copper depletion (CD) inhibits tumor metastases by reducing the number of EPCs and other copper dependent processes in the pre-metastatic niche. These results are an update of our

previously reported study with longer follow-up.⁵

A single arm phase II study of CD with TM enrolled breast cancer (BC) patients who are at high risk for cancer recurrence post-treatment, including those who had node+ triple negative (TNBC), Stage 3, and Stage 4 BC with no evidence of disease (NED). TM was given to maintain ceruloplasmin levels

Continued on p. 18

Continued from p. 17

between 8–16 mg/dl for two years with an extension phase or until relapse. The primary endpoint was change in EPCs measured by flow cytometry before and during treatment. Secondary endpoints included tolerability, safety, PFS and LOXL-2 levels.

Seventy-five patients received 2,778 cycles of TM in the primary and extension study. The primary study treatment duration was 24 cycles (each cycle is 28 days) plus an extension phase. The median age is 51 years (range 29–66). Forty-five patients have stage 2/3 BC, and 30 have Stage 4 BC with NED. Forty-eight percent of patients have TNBC and 40% of patients have Stage 4 NED. Median serum Cp levels were monitored with each cycle. After one cycle, there was a decrease in Cp from 28 to 16 ($p < 0.0001$). Interestingly, TNBC seemed to have a greater decrease from 23.5 to 13 after one cycle. TM was

well tolerated, with grade 3/4 toxicities including: reversible neutropenia (2.3%), febrile neutropenia (0.04%), and fatigue (0.2%). Five-year analysis showed a decrease in EPC's ($p = 0.004$) and LOXL-2 ($p < 0.001$) compared to baseline (Figure 1). At a median follow-up of 7.1 years, the event free survival (EFS) for 75 patients is 71.4%. The EFS for 36 patients with TNBC is 71.7%. EFS for Stage 2/3 TNBC is 83% and for stage IV TNBC is 59.3%. The overall survival for TNBC patients is 80%.

TM is safe, well-tolerated and appears to affect multiple components of the tumor microenvironment identified in pre-clinical models as important for progression. Ongoing studies in banked specimens are underway to further delineate its effect on copper dependent processes necessary for metastases. Randomized trials are warranted, especially in patients who are at high risk for relapse, such as those with TNBC.

REFERENCES

1. Finney L, Vogt S, Fukai T, Glesne D. Copper and angiogenesis: unravelling a relationship key to cancer progression. *Clin Exp Pharmacol Physiol*. 2009;36:88–94.
2. Catena R, Bhattacharya N, El Rayes T, Wang S, Choi H, Gao D, et al. Bone marrow-derived Gr1+ cells can generate a metastasis-resistant microenvironment via induced secretion of thrombospondin-1. *Cancer Discov*. 2013;3:578–89.
3. Erler JT, Bennewith KL, Nicolau M, Dornhofer N, Kong C, Le QT, et al. Lysyl oxidase is essential for hypoxia-induced metastasis. *Nature*. 2006;440:1222–6.
4. Brewer GJ, Dick RD, Grover DK, LeClaire V, Tseng M, Wicha M, et al. Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study. *Clin Cancer Res*. 2000;6:1–10.
5. Chan N, Willis A, Kornhauser N, et al. Influencing the tumor microenvironment: Phase 2 Study of Copper depletion with tetrathiomolybdate in high risk breast cancer and preclinical models of lung metastases. *Clin Cancer Res*. 2017;23(3):666–676.

Effect of Demographic and Psychological Factors on 12 Month Outcomes in Adolescent Bariatric Surgery

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Weight loss surgery is becoming an increasingly utilized treatment option for adolescents with severe obesity. However, there is still limited research on weight loss outcomes for a wide

range of patients. Therefore, the current study aims to investigate the effect of demographic variables (i.e., age, gender, and ethnicity) and pre-surgical mental health on the change in body mass index (BMI) after Laparoscopic Sleeve Gastrectomy (LSG) in the first year following surgery.

This is a retrospective medical chart review of a prospective database of patients who underwent LSG. In this study, N= 196, 75% of patients were female, and their average age was 17 with a standard deviation of 2.45, but ranged from 6–22. Minorities made up 75% of the patient population. The average pre-op BMI of the group was 50.99 with a standard

deviation of 8.67. The mean percent excess BMI lost at 12 months was 53.9% with a standard deviation of 23.7%. Of the 196 patients, 165 patients had pre-surgical mental health evaluations. Of these 165, 28.5% had an anxiety disorder, 46.5% had a depressive/mood disorder, 21.8% had ADHD, and 10.3% had an eating disorder. Change in BMI at three months, six months and 12 months post-op was assessed at post-surgical follow up visits. Demographic variables and mental health diagnoses, evaluated using a structured interview (KSADS), were obtained at the pre-surgical psychological evaluation.

Continued on p. 19

Continued from p. 18

A non-linear Latent Variable Growth Model (LGM) was estimated, including demographic variables and presence/absence of diagnoses in the classes of anxiety, depression, attentional disorders, and eating disorders.

The LGM model showed that change per three months was statistically significant ($r=2.247$, $P<0.001$). Weight loss at three months was significantly associated with weight loss at 12 months ($r=0.892$, $P<0.001$). However, the standardized effect was larger in a model where the latent intercept factor represents the six month outcomes ($I=0.650$), compared to where “I” represents the

three month outcomes ($I=0.516$). This indicates weight loss at six months had a larger influence than weight loss at three months on the weight loss at 12 months. Age, gender, and ethnicity were not associated with three month or 12 month weight loss, or in the rate of weight loss. The presence of a diagnosis of anxiety, depression, or ADHD was not associated with weight loss at any time. However, the presence of a diagnosed eating disorder was associated with less weight loss at three months.

Results of this study indicate that there is no association of demographic variables or most mental health diagnoses with weight loss outcomes following LSG in adolescents. The lack of

a difference in the effect of age serves to mitigate the argument that LSG is not as effective in adolescents under the age of 18 as it is in those over 18. Moreover, presence of a mental health diagnosis should not serve as a contraindication to surgery, but assessment and treatment of disordered eating should remain an important part of preparation for surgery.

Also, the larger effect of the six month change in BMI (as compared to that of three month change in BMI) on the 12 month outcome suggests there may be a window in which patients exhibiting suboptimal BMI change at three months can be identified and an intervention provided to optimize % excess BMI loss.

Effect of Genetic Variation in GSTP1 and AXIN1 on Bone Mineral Density in Children and Young Adults

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Single nucleotide polymorphisms (SNPs) are associated with differential bone mineral density (BMD) measures in humans. Oxidative stress has been implicated in negatively impacting bone quality. The Glutathione S-transferase P 1 (GSTP1) family of enzymes minimize oxidative cellular damage. Studies have shown that variation at rs1695 in GSTP1 negatively impacts BMD.^{1,2} Another determinant in bone quality is the canonical-Wnt

pathway, in which the AXIN1 protein functions as a negative regulator. A 2015 study implicated the rs9921222 variant of AXIN1 as having significant associations with lower total BMD and osteoporosis.³ The present study sought to expand our understanding of the influence of genetic variation in GSTP1 and AXIN1.

Previously assembled DNA samples from The Bone Health cohort (African-American, $n=87$; 46 male, 41 female; ages 5–9) and a Caucasian sub-cohort of the Assessing Inherited Markers of Metabolic Syndrome in the Young (AIMMY) ($n=209$; 102 males, 107 females; ages 18–35) were utilized to measure total BMD without head z-score (adjusted for height) and total BMD, respectively. An Illumina Multi-Ethnic Genotyping Array (MEGA) chip was utilized to genotype the Bone Health cohort, while the Applied Biosystems Taqman

allelic discrimination assays/Applied Biosystems 7900 HT Real-Time PCR were utilized for the AIMMY cohort. Analysis of covariance (ANCOVA) models where genotype was the dependent variable, appropriate phenotype the independent variable, and age (for Bone Health), or age and height (for AIMMY), as covariates were utilized to analyze for genotype-phenotype associations.

A statistically significant association between total BMD and rs1695 was observed in males of the AIMMY Caucasian cohort ($p=0.047$). No significant association between the homozygous GG variant of rs1695 and total BMD was found. No statistically significant genotype-phenotype associations between rs9921222 or rs1695 and total BMD were present in the Bone Health cohort using an additive genetic model. There was no reported

Continued on p. 20

Continued from p. 19

association between total BMD and the rs1695 GG homozygote variant.

This study found a significant association of total BMD and rs1695 AG variant in males from the Caucasian subset of the AIMMY cohort ($p=0.047$). Of note, the homozygous GG minor allele did not demonstrate a significant association with total BMD, despite previous studies reporting otherwise. Significant differences in the association of genetic variants of rs1695 and BMD in both the AIMMY and Bone Health cohorts could be influenced by race/ethnicity — both of which have been significantly associated with bone quality/fracture risk. The significant association present in Caucasian males of the AIMMY cohort ($p=0.047$) but not in females ($p = 0.33$) underscores the

important role of sexual dimorphism in determining musculoskeletal phenotypes. The presence of the rs1695 G allele variant in GSTP1 could indicate appreciable build-up of ROS in males and lower quality of bone.

In contrast to previous studies, our work did not find a significant association with rs9921222 and total BMD or BMD z-score minus head. Conflicting results could be attributed to differences in sample size and demographics, but the highly polygenic nature of BMD makes this a more complicated issue. It is plausible that rs9921222 may be associated with lower total BMD in previous studies because it is in linkage disequilibrium, or inherited with other SNPs associated with lower BMD. The present study could not account for confounding SNPs that may have been inherited along with rs9921222. Future studies

may be able to analyze linkage disequilibrium when establishing associations between rs9921222 and total BMD.

REFERENCES

1. **Malakar SJ, Prezelj J, Marc J.** Testing GSTP1 genotypes and haplotypes interactions in Slovenian post-/pre-menopausal women: novel involvement of glutathione S-transferases in bone remodeling process. *Maturitas*. 2012;71(2):180-7.
2. **Ragab SM, Badr EA, Ibrahim AS.** Evaluation of Glutathione-S-Transferase P1 Polymorphism and its Relation to Bone Mineral Density in Egyptian Children and Adolescents with Beta-Thalassemia Major. *Mediterr J Hematol Infect Ids*. 2016;8(1).
3. **Warrington NM, Kemp JP, Tilling K, Tobias JH, Evans DM.** Genetic variants in adult bone mineral density and fracture risk genes are associated with the rate of bone mineral density acquisition in adolescence. *Hum Mol Genet*. 2015;24(14):4158-66.

Pupillometric Assessment of Small Doses of Opioid in a Pediatric Population

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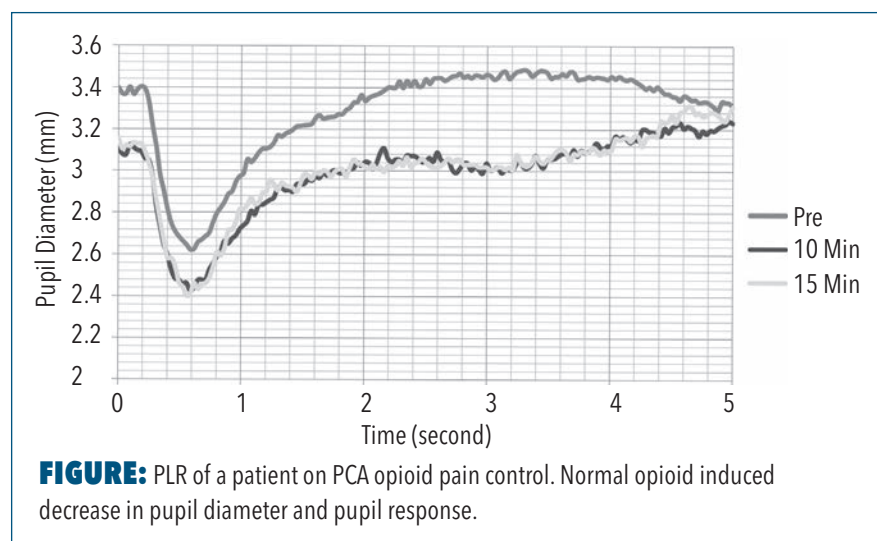
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Opioid prescriptions in the United States have more than tripled from 1999–2014, during which there has been a staggering increase in opioid-involved drug overdose deaths.¹ Physician prescribing patterns are thought to be a major contributory factor to the increase in drug overdose



in America, as four out of five new heroin users started by misusing prescription painkillers.² Providers need the means to objectively monitor analgesic efficacy of treatment in patients

with pain to mitigate unnecessary analgesic prescriptions.

Continued on p. 21

It is well established that mu opioid agonists like morphine cause miosis, an effect that does not exhibit tolerance.³ This suggests utility in investigating pupil size and responsiveness as pharmacokinetic measures of bioavailability. An infrared pupillometer is a device that produces a short light stimulus and subsequently measures parameters of the pupillary light reflex (PLR) including maximum and minimum pupil size (MAX, MIN), maximum constriction velocity (MCV), latency period before constriction onset (LAT), change in pupil size (DELTA), and average constriction velocity (ACV). Current data support the efficacy of using infrared pupillometry to detect high dose opioid presence, but no research exists judging its efficacy in monitoring low dose therapeutic levels.⁴ Patient controlled analgesia (PCA) is widely used for pediatric inpatients due to advantages associated with patient autonomy through self-administration and maintenance of steady state, as the dose for each pump is low and is equipped with a max-out setting.⁵

In our IRB approved study, we enrolled 15 patients between the ages of 7 and 18 on the pain medicine service receiving low dose morphine (n=12) or hydromorphone (n=3) on PCA. The patients were either post-surgical or admitted for sickle cell vasoocclusive crisis. The pupillometer was used to take a baseline PLR (Figure 1), and repeated measures were taken 10 and 15 minutes post-PCA dose infusion, which was administered at the patient's discretion.

A repeated measures ANOVA using GraphPad Prism version 7.00c was conducted to compare the effect of the opioid on specific parameters of the PLR. There was a significant

Effect	Dfn, Dfd	F Statistic	p-Value	R ²
MAX (Maximum Pupil Size)	1.222, 17.11	11.68	0.0021	0.4548
MIN (Minimum Pupil Size)	1.211, 16.95	10.3	0.0036	0.4239
DELTA (Change in Pupil Size)	1.442, 20.18	1.775	0.1989	0.1125
LAT (Latency period before onset of constriction)	1.882, 26.35	3.746	0.0393	0.2111
ACV (Average Constriction Velocity)	1.764, 24.7	2.326	0.1239	0.7908
MCV (Maximum Constriction Velocity)	1.934, 27.08	3.414	0.0490	0.1961

TABLE: Repeated Measures ANOVA evaluating the significance of all pupillary parameters baseline vs. post-PCA dosing

effect of the opioid on the MAX, MIN, LAT and MCV parameters (Table 1). Post hoc tests found that the 10 and 15 minute time points were significantly smaller than the baseline for the parameters MAX ($p=.0016$, $p=.0010$) and MIN ($p=.0250$, $p=.0070$). Additionally, it was found that LAT was significantly longer from baseline at the 15-minute measure ($p=.0350$), and there was a significant difference between the 10 and 15 minute time points for the MIN ($p=.0251$).

This evidence supports the use of the pupillometer in evaluating opioid pharmacologic activity and patient sensitivity. Furthermore, in concordance with previous research, the MIN is significantly correlated with opioid concentration dose-dependently across the 15-minute measurement window. Before applying the pupillometer to clinical pain medicine, more research needs to be done comparing pupillometric parameters to blood levels of opioid metabolites. With detection limits, providers could use this tool to monitor treatment efficacy and optimize opioid administration schedules based on patient physiology, rate of metabolism, and previous opioid use. One specific application could eliminate the need for genetic testing for CYP2D6

polymorphisms, instead using the pupillometer to assess pharmacologic activity following a small dose. Developing noninvasive ways to objectively measure the effects of opioid medications will help clinicians more responsibly prescribe these drugs that have been so widely abused over the last 20 years.

REFERENCES

- Centers for Disease Control and Prevention. Annual Surveillance Report of Drug-Related Risks and Outcomes — United States, 2017. Surveillance Special Report. U.S. Department of Health and Human Services. Published August 31, 2017. Accessed Oct. 4, 2017, at <https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report>.
- Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002–04 and 2008–10. *Drug Alcohol Depend.* 2013;132(1-2):95–100.
- Collette, B-J. Opioid tolerance: the clinical perspective. *British Journal of Anaesthesia.* 1998; 81: 58–68.
- Rollins MD, Feiner JR, Lee JM, Shah S, Larson M. Pupillary effects of high-dose opioid quantified with infrared pupillometry. *Anesthesiology.* 121 2014, pp. 1037–1044
- McDonald A, Cooper MG. Patient-controlled analgesia: an appropriate method of pain control in children. *Pediatric Drugs.* 3 2001, pp. 273–284

Characterization of Pediatric Bowel and Bladder Dysfunction via Pupillometry

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Bowel and Bladder Dysfunction (BBD) refers to a heterogeneous group of voiding disorders, accounting for an estimated 40 percent of pediatric urology visits.¹ Symptoms of BBD include enuresis, urgency, and urinary retention, often accompanied by constipation. While the role of the autonomic nervous system (ANS) in regulation of voiding is well-characterized, it is not known if children presenting with BBD exhibit distinct patterns of ANS activity that could be measured for diagnosis or targeted for intervention.

Pupillometry allows for assessment of systemic ANS activity, and therefore could elucidate differences in ANS function among BBD patients. This study aimed to determine whether a pupillary response can be characterized for BBD. Eight pupillary light reflex (PLR) parameters were assessed and compared to controls.

The goal of this study was to use pupillometry to compare the pupillary responses of BBD patients to controls pre- and post-voiding. Hypotheses were:

- 1. BBD patients will show a distinct pattern of ANS activity relative to controls.

	MAX	MIN	DELTA	LAT	ACV	MCV	ADV
Pre-voiding	0.035395	0.098949	0.342316	0.331814	0.056367	0.139481	0.175263
Post-voiding	0.069649	0.178029	0.224430	0.096806	0.256561	0.120460	0.310756

TABLE 1: P-values from T-tests of pupillary parameters among BBD patients compared to controls.

- 2. BBD patients will show different changes in ANS activity before and after voiding relative to controls.

The Neuroptics PLR-2000 pupilometer was used to assess eight pupillary parameters. Both BBD patients and controls were recruited from the urology clinic at Children's National. Using scores from the Dysfunctional Voiding and Incontinence Scoring System (DVISS) questionnaire, subjects were identified as BBD patients (score of 9 or higher; n=10) or control patients (score of 8 or lower; n=8). Pupillometry was then conducted before and after voiding.

BBD patients showed a significantly larger maximum pupil size in the pre-voiding condition relative to controls (Table 1). Additionally, several pre- and post-voiding parameters showed near-significant differences. The changes in values pre- and post-voiding were also compared, and BBD patients showed significantly larger changes in both minimum pupil size and in average constriction velocity (ACV) (Table 2). These results suggest that BBD patients may have a distinctive profile of ANS activity, and that this profile may be detectable in a clinical setting via pupillometry.

The role of the autonomic nervous system in voiding behavior is well described, with the parasympathetic nervous system (PNS) generally more active during voiding, and the sympathetic nervous system (SNS) more active during the retention phase in healthy patients.

The larger maximum pupil size seen in the pre-voiding condition among BBD patients could indicate higher SNS activity, or lower PNS activity, during the retention phase. This is consistent with a finding from a study of cardiac autonomic activity among BBD patients, which found higher baseline heart rates relative to controls, consistent with relatively higher SNS activity.¹

Additionally, the significantly larger changes in minimum pupil size and average constriction velocity between pre- and post-voiding conditions among BBD patients could indicate greater variability in ANS activity related to voiding behavior. The results could be applied toward a diagnostic tool for identify patients with BBD dysautonomia, versus patients with behavioral, anatomical, or other causes of urinary symptoms.

Continued on p. 23

REFERENCES

1. Fazeli MS, Collet JP, MacNeily AE, Afshar K. Cardiac autonomic nervous system activity in children with bladder and bowel dysfunction. *The Journal of Urology*. 2016; 1245–1249.

MAX	MIN	DELTA	LAT	ACV	MCV	ADV
0.126567	0.015353	0.159828	0.097724	0.042967	0.482969	0.133028

TABLE 2: P-values from T-tests of change in pupillary parameters post-voiding among BBD patients compared to controls. Max = maximum pupillary diameter; MIN = minimum pupillary diameter; DELTA = change in pupillary diameter; LAT = latency; ACV = average constriction velocity; MCV = maximum constriction velocity; and ADV = average dilation velocity.

PPARGC1A and IGF Polymorphisms Correlate with Greater Strength Performance in Healthy Young Adult Caucasian Cohorts

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Extensive variation in skeletal muscle strength has been attributed to a combination of genetic and environmental factors. Recent studies show that favorable single nucleotide polymorphisms (SNPs) in PPARGC1A and Insulin-like Growth Factor 1 (IGF-1) genes correlate with greater power sport performance in professional athletes.^{1,2} In rs8192678 on the PPARGC1A gene, a substitution of adenine (A) for guanine (G) causes serine (Ser) to replace glycine (Gly) resulting in lower PGC-1 α expression and reduced performance.¹ For an IGF-1 rs7136446 polymorphism, GG homozygosity correlates with greater expression of IGF-1 and increased maximal force.³ The purpose of the study was to investigate whether these

SNP	Phenotype	Gender	N; adjusted mean \pm SEM	Significantly different genotypes
PPARGC1A	% change in 1-RM strength (D)	Female	GG (N=171; 11.69 \pm 3.06)* AG (N=210; 13.35 \pm 2.76)** AA (N=54; 32.52 \pm 5.44)* **	*p=0.0027 **p=0.0054
PPARGC1A	Baseline 1-RM strength (D)	Male	GG (N=136; 29.89 \pm 0.52)* AG (N=162; 28.91 \pm 0.47) AA (N=35; 27.08 \pm 1.02)*	*p=0.0432
IGF1 (rs7136446)	Baseline isometric strength (ND)	Female	AA (N=94; 58.25 \pm 2.29)* GA (N=122; 67.00 \pm 2.02)* GG (N=48; 62.27 \pm 3.22)	*p=0.0134
IGF1 (rs7136446)	Baseline isometric strength (D)	Female	AA (N=94; 61.34 \pm 2.33)* GA (N=122; 69.58 \pm 2.05)* GG (N=48; 66.22 \pm 3.28)	*p=0.0256
IGF1 (rs7136446)	% change in isometric strength (ND)	Male	AA (N=61; 20.01 \pm 2.55) GA (N=66; 15.92 \pm 2.44)* GG (N=34; 26.37 \pm 3.42)*	*p=0.0411
IGF1 (rs7136446)	% change in isometric strength (D)	Male	AA (N=60; 6.79 \pm 2.04) GA (N=65; 2.39 \pm 1.95)* GG (N=34; 12.09 \pm 2.71)*	*p=0.0125

TABLE 1: Significant genotype / phenotype association found in FAMuSS; Additive model

polymorphisms predict strength performance in young Caucasian adults who are not elite athletes.

Functional Single Nucleotide Polymorphism Associated with

Human Muscle Size and Strength (FAMuSS) consisted of healthy young adult Caucasians who participated

Continued on p. 24

in a three-month strengthening program of their non-dominant (ND) arm (males: $n=165$, females: $n=276$, avg. age= 23 years). Baseline strength and percent change in strength after training were measured. The Assessing Inherited Markers of Metabolic Syndrome in the Young (AIMMY) University of Calgary Caucasian sub-cohort was composed of young adults (male $n=102$, female $n=107$, avg. age= 23 years). Grip strength and oxygen consumption (VO_2 Max) were measured. Allele frequencies were calculated and tested, and outcomes were separated by sex using analysis of covariance. Where the overall ANCOVA F-test was statistically significant, post hoc pair-wise comparisons were performed and the p-values were adjusted using the Sidak method.

FAMuSS Genotype distributions for PPARGC1A were found to be in Hardy-Weinberg equilibrium. Although IGF-1 was not in Hardy Weinberg equilibrium, the distribution of alleles was similar to a prior study of IGF1 gene variants⁴ and was not excluded. AIMMY: Genotype distributions for IGF-1 and PPARGC1A were found to be in Hardy-Weinberg equilibrium.

Our study expands our understanding of the roles rs8192678 and rs7136446 play in anaerobic exercises. Previous research of PPARGC1A in endurance athletes found a lower frequency of the Ser allele correlates with greater aerobic performance,

but that the Ser/Ser genotype was more common among powerlifter athletes.¹ We found that while Ser/Ser genotype females had a greater percentage change in 1-RM strength in the D arm, there was no statistically significance of the Ser/Ser genotype regarding baseline strength, percentage change in 1-RM strength of the ND arm, or percentage change of isometric strength. In male participants, the Gly/Gly genotype was more beneficial to baseline 1-RM strength. Our study found no significant associations for variants of rs8192678 with VO_2 max. The results indicate a potential sexually dimorphic effect.

Genetic variants resulting in higher expression of IGF-1 have been associated with greater muscular strength responses to anaerobic training as well as greater aerobic performance². We focused on genetic variation in rs7136446 impacted strength and anaerobic exercise. We found that male G/G individuals had a greater percent change in isometric strength than heterozygous individuals. Females with at least one G allele had a greater baseline isometric strength and VO_2 max. Our results support earlier findings of correlation

with greater maximal force production³ and indicate a sexually dimorphic effect.

Variation in rs8192678 and rs7136446 may help predict individual response to an exercise program, particularly in females. The ability to better predict response would play a significant role when choosing more effective exercise and physical therapy programs.

REFERENCES

1. Gineviciene V, Jakaitiene A, Aksenow MO, et al. Association analysis of ACE, ACTN3 and PPARGC1A gene polymorphisms in two cohorts of European strength and power athletes. *Biol Sport*. 2016; 33(3):199-206.
2. Ben-Zaken S, Malach S, Meckel Y, et al. Frequency of the IGF A/G rs7136446 Polymorphism and Athletic Performance. *Acta Kinesiologiae Universitatis Tartuensis*. 2016; 22: 36-46.
3. Huuskonen A, Lappalainen J, Oksala N, et al. Common Genetic Variation in the IGF1 Associates with Maximal Force Output. *Medicine & Science in Sports & Exercise*. 2011; 43: 2368-2374.
4. Rzehak P, Grote V, Lattka E, et al. Associations of IGF-1 gene variants and milk protein intake with IGF-1 concentrations in infants at age 6 months- results from a randomized clinical trial. *Growth Hormone & IGF Research*. 2013; 23:149-158.

SNP	Phenotype	Gender	N; adjusted mean \pm SEM	Significantly different genotypes
IGF1 (rs7136446)	Height	Males	TT (N=34; 178.69 \pm 1.17) CT (N=29; 183.08 \pm 1.27)* CC (N=9; 178.89 \pm 2.27)	*p=0.0388

TABLE 2: Significant genotype / phenotype associations found in AIMMY (Caucasian subcohort); Additive model

Risk Assessment and Management of Children with Congenital Heart Diseases Undergoing Non-Cardiac Surgery

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Congenital heart disease (CHD) is the most common birth defect¹ with an incidence of 1%, or about 40,000, births per year.³ Patients with CHD are at increased risk of cardiac arrest and mortality during anesthesia and surgery owing to several factors like anesthetic agents depressing cardiac function and reducing blood pressure, which further impairs cardiac function. Many of these patients have Trisomy 21 and other syndromes that further complicate anesthetic care owing to difficult airway management, difficult vascular access, and respiratory compromise. Due to these conditions, vigilance and attention to detail and the ability to react rapidly to physiologic changes is required throughout the course of anesthesia.⁵

Faraoni et. al in 2016 published a study further looking into post-operative outcomes in children with and without CHD undergoing non-cardiac surgery. Patients with major CHD had a mortality rate of 3.6% and those with severe CHD had a mortality rate of 8.2%. They found that children with severe CHD had an increased risk of 30-day mortality with an odds ratio of 8.43. They also found that major and severe CHD children also had higher rates of reintubation compared to non-CHD patients with odds ratio of 3.11

and 2.46. Severe CHD children had higher cardiac arrest rates.

Children's National Health System (Children's National) has a specialized Cardiac Anesthesia division that specializes in the care of children with CHD. Patients with CHD who require surgery undergo thorough and comprehensive risk stratification by a pediatric cardiac anesthesiologist prior to any surgery. It includes a review of preoperative clinical data and preoperative medication management, formulation of an appropriate anesthetic plan, and determination of postoperative disposition. Patients deemed moderate and high-risk are cared for by the cardiac anesthesia team, allowing highly specialized anesthesia care for complicated cases.

We investigated the impact on care with the formation of the specialized Cardiac Anesthesia division on perioperative outcomes for non-cardiac surgery. A retrospective study assessed the management of these CHD patients. A group of patients who had CHD and underwent non-cardiac surgery were selected, and categorized according to the ACS NSQIP Pediatric Risk Calculator. For each patient, their intraoperative cardiac arrest rate, reintubation rate, and 30-day mortality were gathered and analyzed.

Out of the 131 CHD patients undergoing non-cardiac surgery seen by the Cardiac Anesthesia division, 13 had mild CHD, 58 had major CHD, and 58 had severe CHD. Within this patient population, there was an intraoperative cardiac arrest rate of 0.8%, postoperative cardiac arrest rate of 2.3%, reintubation rate of 3.9%, 30-day mortality of 1.8% among major CHD

patients, and 30-day mortality among severe patients of 12%.

The cardiac anesthesia team at Children's National cared for a large number of major and severe CHD patients. The use of a specialized cardiac anesthesia team in the management of such complex patients led to a low incidence of perioperative cardiac arrest and reintubation compared to other literature, such as Ramamoorthy's study. Patients with severe CHD continued to have a high rate of 30-day mortality. The main limitation of this study is the lack of a true control group for comparison. While this study suggests that using a specialized team in the management of complex high-risk cardiac patients leads to improved outcomes, a prospective study is needed for confirmation.

REFERENCES

- 1 Congenital Heart Defects (CHDs). (2016, Aug. 1). CDC. Retrieved August 13, 2017, at <https://www.cdc.gov/ncbddd/heartdefects/data.html>
- 2 Faraoni D, Zurkowski D, Vo D, Goobie SM, Yuki K, Brown ML, DiNardo JA. Post-operative outcomes in children with and without congenital heart disease undergoing non-cardiac surgery. *Journal of the American College of Cardiology*, 67(7), 2016;793-801.
- 3 Hoffman JL, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890-1900.
- 4 Ramamoorthy C, Haberkern CM, Bhananker SM, Domino KB, Posner KL, Campos JS, Morray JP. Anesthesia-related cardiac arrest in children with heart disease: data from the Pediatric Perioperative Cardiac Arrest (POCA) registry. *Anesthesia & Analgesia*, 110(5). 2010;1376-1382.
- 5 Sümpelman, R, Osthaus WA. The pediatric cardiac patient presenting for noncardiac surgery. *Current Opinion in Anesthesiology*, 20(3). 2007;216-220.

Optical Coherence Tomography Angiography Imaging of Choriocapillaris in Patients with Age-Related Macular Degeneration

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Age-related macular degeneration (AMD) is the leading cause of blindness in people 55 years and older in developed countries. While the pathophysiology of AMD has primarily been attributed to oxidative stress and inflammatory pathways, there is evidence of a vascular contribution to the disease pathogenesis, including choroidal hypoperfusion and choriocapillaris vascular density dropout. However, it is unknown if decreased choroidal circulation is a contributory effect to AMD or a secondary effect of AMD progression.⁴ Optical coherence tomography angiography (OCTA) can be used to better understand how alterations or breakdown in the choriocapillaris vessel network of the choroid may precipitate and contribute to the development of choroidal neovascular, or “wet,” AMD.

In histological studies of retinal drusen, vascular density beneath drusen has been found to be 45% lower than areas adjacent to drusen.⁵ This study seeks to use noninvasive methods to evaluate the angiographic flow of the choriocapillaris in drusen subjects to elucidate early vascular morphologic changes that may influence AMD progression. The most

commonly used vascular diagnostic imaging methods in ophthalmology are fluorescein angiography (FA) and indocyanine green angiography (ICGA). Recent advances in optical coherence tomography (OCT) imaging have led to the development of OCTA methods that do not require injection of a fluorophore.

Retinal imaging was performed on nine subjects including four AMD patients, three age-matched normal subjects over 70-years old, and two normal subjects less than 40 years old. Retinal imaging was acquired using a swept-source OCT system with a Fourier-Domain Mode-Locked laser. Phase-variance OCTA image processing was performed after data acquisition of multiple repeat B-scans collected in a series of images with temporal variation. Phase images were then corrected for by sub-pixel motion of the whole sample by bulk-phase removal. The variance of the phase as a set of vectors can then be interpreted as angiographic contrast. This enables choriocapillaris retinal microvasculature imaging from the

three-dimensional OCTA data.

Regions of interest (ROIs) selected for a 10 μ m thick slab of choriocapillaris microvasculature were then analyzed for mean signal intensity as a measure of angiographic vessel density. Qualitative assessment of en face choriocapillaris projection images from a subject with drusen and AMD demonstrate choriocapillaris dropout seen with progression of AMD, in comparison to the intact microvascular choriocapillaris demonstrated in the normal subject (Figure 1).

Phase-variance angiographic signal intensity was significantly decreased by over 38% in the drusen subjects in comparison to all normal subjects (39.98 vs. 64.64, $p < 0.001$).

Decreased choriocapillaris signal intensity seen in the presence of drusen demonstrates a pathogenic change in vasculature with AMD from those seen in the normal aging process. Quantitative and qualitative analysis of choriocapillaris using OCTA can help further elucidate

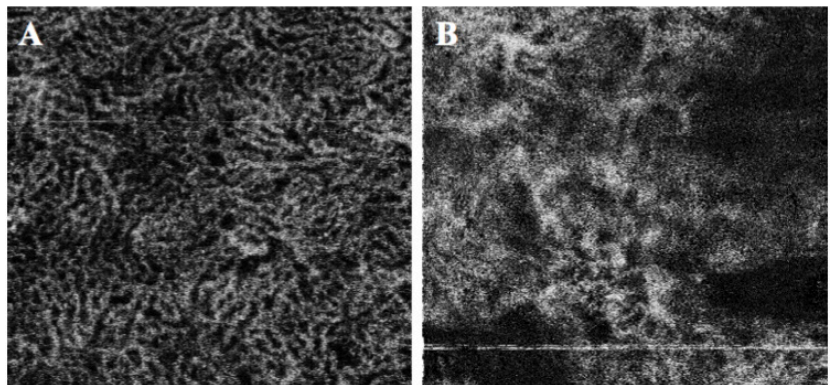


FIGURE 1: OCTA of choriocapillaris in A) normal, and B) AMD subjects.

Continued on p. 27

Continued from p. 26

AMD disease pathogenesis and progression. Detection of choriocapillaris vascular changes without the need for injection of a fluorophore with FA or ICGA offers a safe, non-invasive imaging modality with improved ability to render microvascular detail in three-dimensional data acquisitions. In the setting of choroidal neovascularization, patients can then utilize anti-vascular endothelial growth factor injection therapy earlier in the course of wet AMD progression with improved preservation of vision.

REFERENCES

1. Curcio C, Johnson M, Rudolf M, Huang J. The oil spill in ageing Bruch membrane. *British Journal of Ophthalmology*. N.d.;95(12):1638-1645.
2. Mettu PS, Wielgus AR, Ong SS, Cousins SW. Retinal pigment epithelium response to oxidant injury in the pathogenesis of early age-related macular degeneration. *Mol Aspects Med*. 2012;33(4):376-398.
3. Bhutto I, Luty G. Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. *Mol Aspects Med*. 2012;33(4):295-317.
4. Mullins R, Johnson M, Faidley E, Skeie J, Huang J. Choriocapillaris Vascular Dropout Related to Density of Drusen in Human Eyes with Early Age-Related Macular Degeneration. *Investigative Ophthalmology & Visual Science* [serial online]. N.d.;52(3):1606-1612.
5. Mullins RE, Johnson MN, Faidley EA, et al. Choriocapillaris Vascular Dropout Related to Density of Drusen in Human Eyes with Early Age-Related Macular Degeneration. *Invest Ophthalmol Vis Sci*. 2011;52:1606-1612.

CHORINOCAPILLARIES PHASE-VARIANCE ANGIOGRAPHIC SIGNAL INTENSITY

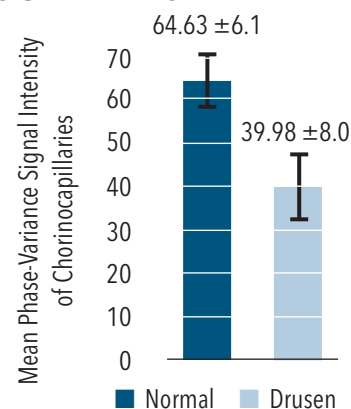


FIGURE 2: Average choriocapillaries phase-variance angiographic signal intensity in drusen and normal subjects

Pushing the Limits: Perinatal Outcomes Beyond Prolonged Second Stage

To evaluate whether extremely prolonged second stage of labor in nulliparous women affects maternal and neonatal outcomes.

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We performed a retrospective cohort study of term, nulliparous women with singleton gestations, cephalic presentation, epidural anesthesia, in labor, who reached 10 centimeters of cervical dilation. Exclusion criteria were intrauterine fetal demise,

Continued on p. 28

	Normal Second Stage (NSS) 0-179 minutes (referent) n = 430	Prolonged Second Stage (PSS) 180-299 minutes n = 116	NSS vs PSS OR (95% CI) P value	Extremely Prolonged Second Stage (EPSS) ≥ 300 minutes n = 115	NSS vs EPSS OR (95% CI) P value
Maternal Outcomes					
Cesarean Delivery	9 (2.1)	5 (4.3)	2.10 (0.63-6.41)	34 (29.6)	19.47 (9.22 - 44.43)
Vaginal Delivery	421 (97.9)	111 (95.7)	0.48 (0.16-1.59)	81 (70.4)	0.05 (0.02-0.11)
Spontaneous Vaginal Delivery	401 (93.3)	100 (86.2)	0.45 (0.24-0.88)	58 (50.4)	0.07 (0.04-0.12)
Operative Vaginal Delivery	20 (4.6)	11 (9.5)	2.14 (0.96-4.59)	23 (20.0)	5.10 (2.68-9.79)
Chorioamnionitis	23 (5.3)	9 (7.8)	1.49 (0.64-3.26)	10 (8.7)	1.68 (0.75-3.80)
Endometritis	1 (0.2)	0 (0.0)	NE	0 (0.0)	NE
Postpartum hemorrhage	26 (6.0)	8 (6.0)	1.15 (0.47-2.55)	36 (31.3)	7.04 (4.03-12.44)
Transfusion	0 (0.0)	0 (0.0)	NE	1 (0.8)	NE
3 rd degree perineal laceration	14 (3.3)	10 (8.6)	2.80 (1.17-6.51)	9 (7.8)	2.52 (1.02-5.99)
4 th degree perineal laceration	1 (0.2)	0 (0)	NE	1 (0.9)	NE
Neonatal Outcomes					
Shoulder dystocia	7 (1.6)	2 (1.7)	1.06 (0.15-4.83)	4 (3.5)	2.17 (0.55-7.63)
Birth weight, grams	3246 ± 416	3392 ± 447	-	3497 ± 422	0.2
NICU admission	12 (2.8)	2 (1.7)	0.61 (0.09-2.46)	4 (3.5)	1.26 (0.34-3.82)
CPAP or greater	21 (4.9)	5 (4.3)	0.88 (0.29-2.28)	16 (13.9)	3.14 (1.56-6.26)
Sepsis	3 (0.7)	0 (0.0)	NE	1 (0.9)	1.25 (0.13-12.11)
HIE	2 (0.5)	0 (0.0)	NE	1 (0.9)	1.86 (0.167-20.65)
Seizure	1 (0.2)	0 (0.0)	NE	0 (0.0)	NE
Perinatal mortality	1 (0.2)	0 (0.0)	NE	0 (0.0)	NE
Composite Neonatal Outcome	47 (10.9)	9 (7.8)	0.69 (0.31-1.40)	27 (23.5)	2.50 (1.60-4.23)

Abbreviations: CI- confidence interval, SD- standard deviation, NE- not estimable, NICU- neonatal intensive care unit, CPAP- continuous positive airway pressure, HIE- hypoxic ischemic encephalopathy
Data are n (%) or mean ± standard deviation

TABLE 1: Selected Maternal and Neonatal Outcomes

planned cesarean delivery, or suspected major fetal anomaly. Women were compared by length of second stage: 0-179 minutes (normal second stage), 180-299 minutes (prolonged second stage) and ≥ 300 minutes (extremely prolonged second stage). Primary outcome was incidence of spontaneous vaginal delivery (SVD). Maternal and neonatal outcomes were compared as secondary outcomes.

In total, 662 women were evaluated: 115 with extremely prolonged second stage (EPSS), 116 with prolonged second stage (PSS) and 430 with normal second stage (NSS). Maternal demographics differed by age, race, gestational age, diabetes and epidural use. Incidence of SVD was 93.3% (401/430) in the NSS group, 86.2% (100/116) in the PSS group, and 50.4% (58/115) in the EPSS group (RR 0.45, 95% CI 0.22-0.93) (Table 1). The PSS group had a higher incidence of 3rd degree laceration: 8.6% (10/116) vs 3.3% (14/430) in the NSS group (OR 2.80; 95% CI 1.17-6.51). The EPSS group had a higher incidence of postpartum hemorrhage compared to the NSS group: 31.3% (36/115) vs 6.0% (26/430) (OR 7.04; 95% CI 4.03-12.44), 3rd degree laceration: 7% (9/115) compared to 3.3% (14/430) in the NSS

	Normal Second Stage (NSS) 0-179 minutes (referent) n = 430	Prolonged Second Stage (PSS) 180-299 minutes n = 116	Extremely Prolonged Second Stage (EPSS) ≥ 300 minutes n = 115	p
Maternal Age, years	30.2 \pm 5.8	31.5 \pm 5.8	33.4 \pm 5.2	0.004
Ethnicity (non-Hispanic)	380 (88.4)	99 (85.3)	100 (87.0)	0.8
Race				<0.001
Non-Hispanic white	216 (50.2)	74 (64.0)	71 (61.7)	
Non-Hispanic black	152 (35.3)	21 (18.1)	21 (18.2)	
Asian	28 (6.5)	7 (6.0)	13 (11.3)	
Other	31 (7.2)	10 (8.6)	10 (8.7)	
Diabetes				<0.001
Diabetes: gestational	19 (4.4)	4 (3.4)	12 (10.4)	
Diabetes: pregestational	0 (0)	3 (2.6)	0 (0.0)	
Hypertension				0.4
Chronic hypertension	3 (0.7)	1 (0.9)	4 (3.5)	
Gestational hypertension	11 (2.6)	2 (1.7)	2 (1.7)	
Preeclampsia	32 (7.4)	8 (6.9)	12 (10.4)	
Superimposed preeclampsia	3 (0.7)	1 (0.9)	0 (0.0)	
BMI at delivery, kg/m ²	29.9 \pm 5.1	28.2 \pm 5.1	29.1 \pm 4.6	0.9
Gestational Age at delivery, weeks	39.6 \pm 1.2	39.9 \pm 1.2	39.9 \pm 1.2	<0.001
Induction	109 (25.3)	33 (28.4)	37 (32.2)	0.3
Epidural	284 (66.0)	101 (87.1)	107 (93.0)	<0.001
Fetal Position				
Occiput Anterior	230 (53.5)	60 (51.7)	51 (44.3)	<0.001
Occiput Posterior	15 (3.7)	8 (6.9)	21 (18.2)	
Occiput Transverse	5 (1.2)	3 (2.9)	4 (3.5)	

Abbreviations: SD - standard deviation; BMI - body mass index; OVD - operative vaginal delivery; When data does not = 100%, this is due to missing data

TABLE 2: Maternal, Obstetric, and Neonatal Characteristics by Length of Second Stage

group, (OR 2.52; 95% CI 1.02-5.99) neonatal CPAP use: 13.9% (16/115) vs 4.9% (21/430) in the NSS group (OR 3.14; 95% CI 1.56-6.26) and composite neonatal outcome: 23.5% (27/115) vs 10.9% (47/430) in the NSS group (OR 2.50; 95% CI 1.60-4.23).

In nulliparous term women with singleton gestations who reached 10 centimeters cervical dilation, the chance of spontaneous vaginal delivery decreased by 55% after three hours of second stage and by 97% after

five hours of second stage. However, most women delivered vaginally, with 70.4% of women delivering by SVD after five hours. The PSS group had similar maternal and neonatal outcomes as the NSS group; whereas the EPSS group had significantly worse maternal and composite neonatal outcomes. Risks and benefits of PSS vs. EPSS should be weighed during clinical decision making on how long to continue labor during the second stage.

Tracheal Aspirate Cultures in Intubated Neonates: A Descriptive Epidemiological Cohort Study

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Up to 50% of antibiotic use in pediatric intensive care units is for empiric treatment of ventilator-associated pneumonia (VAP).¹ Positive tracheal aspirate culture results could represent colonization or infection, and cultures may be positive in clinically asymptomatic patients.² A better understanding of the clinical factors that lead to the ordering of tracheal aspirate cultures and antibiotic prescription in the setting of positive tracheal aspirate cultures could help us optimize clinical practice.

We conducted a retrospective cohort study of intubated neonates admitted to Children's National Health System (Children's National) neonatal intensive care unit (NICU) who had tracheal aspirate cultures sent between May 2016 and December 2016. Through chart review, we identified clinical factors in the 48 hours preceding tracheal aspirate culture order. These included vital sign changes, change in respiratory secretions, increase in ventilator setting or oxygen requirement, white blood cell count, C-reactive protein (CRP), and chest X-ray results. Outcome measures collected include hospital length of stay, NICU length

	Overall (n = 51)	No Growth / normal flora (n = 32)	Positive for pathogens (n = 19)
Fever	0/51 (0%)	0/32 (0%)	0/19 (0%)
Hypothermia	10/51 (20%)	6/32 (19%)	1/19 (5%)
Leukocytosis	18/51 (35%)	11/32 (34%)	7/19 (36%)
Leukopenia	3/51 (6%)	1/32 (3%)	2/19 (11%)
Change in secretions	7/51 (14%)	1/32 (3%)	6/19 (32%)
Increase Vent Settings	11/51 (22%)	6/32 (19%)	5/19 (26%)
Increase O2 Requirements	11/51 (22%)	4/32 (13%)	7/19 (37%)
Elevated CRP	18/51 (35%)	11/32 (34%)	7/19 (37%)
Tachycardia	10/51 (20%)	0/32 (0%)	6/19 (31%)
Hemodynamic Instability	31/51 (61%)	22/32 (69%)	9/19 (47%)

FIGURE: Clinical factors noted around time of respiratory culture

of stay, ventilator days, discharge on respiratory support, recurrence of respiratory infection, bronchopulmonary dysplasia, colonization with multidrug-resistant organism (MDRO), and mortality.

We identified 51 intubated neonates who met inclusion criteria. Preterm infants accounted for 84%, with a median preterm gestation of 28 weeks. In the 48 hours preceding the culture, patients demonstrated hemodynamic instability (61%), leukocytosis (35%), increase in ventilator settings (22%), increase in oxygen requirement (22%), change in secretions (14%), and elevated CRP (35%).

A pathogen was identified in 37% of isolates. *S. aureus* (7) was the most frequently isolated pathogen, followed by *K. pneumoniae* (5) and *Enterobacter* spp. (4). Antibiotics were prescribed for 88% of patients. The most frequently prescribed antibiotic was vancomycin (67%) followed by gentamicin (63%). The median

number of antibiotic days of therapy around the time of culture (+/- 1 week) was 14 (IQR: 6, 16).

There is considerable variability in the clinical factors noted around the time of respiratory culture. Fewer than half of respiratory cultures identified a pathogen. Antibiotic courses were prescribed for most (88%) patients.

REFERENCES

1. Foglia E, Meier MD, Elward A. Ventilator-Associated Pneumonia in Neonatal and Pediatric Intensive Care Unit Patients. *Clinical Microbiology Reviews*, 20(3). 2007;409-425. doi:10.1128/cmr.00041-06
2. Willson DF, Conaway M, Kelly R, Hendley JO. The Lack of Specificity of Tracheal Aspirates in the Diagnosis of Pulmonary Infection in Intubated Children. *Pediatric Critical Care Medicine*, 15(4), 2014;299-305. doi:10.1097/pcc.000000000000106

Lapse in In-Line Stabilization in Pediatric Trauma Patients

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Cervical spine (C-spine) injuries occur in 1.5% of injured children sustaining blunt injuries who are seen at a trauma center, with a mortality rate approaching 20%.^{1,2} To prevent worsening of a C-spine injury in at-risk patients, the neck should be immobilized in a “neutral position” to minimize movement until it can be examined. We previously observed that failure to maintain C-spine stabilization is a frequent error during pediatric trauma resuscitations.³

The objectives were to identify the different types of lapses in C-spine stabilization during trauma resuscitations and to determine tasks associated with the lapses. Our secondary objective was to evaluate patient and resuscitation features associated with lapses in C-spine stabilization.

Fifty-six videos of trauma resuscitations performed at Children's National Health System were

reviewed to identify lapses in C-spine stabilization. Patient features, including Glasgow-Coma Scale (GCS) motor score, and resuscitation features, including time of resuscitation (weekday vs. weekend), were obtained from the trauma database and medical chart review. Tasks associated with lapses were identified through video review. The presence, duration, and number of lapses were analyzed using logistic and linear regression models for associations with patient and resuscitation features.

Two types of lapses were observed: incorrect in-line stabilization C-spine (n=52, 75.4%) and complete lapse in stabilization (n=17, 24.6%). The most common task performed during a lapse was C-spine collar manipulation (n=43, 50.6%). C-spine collar manipulation was associated with a higher likelihood of a lapse (OR 6.82; 95% confidence interval (CI) 1.74, 26.64; $p < 0.01$). The lapse duration decreased by 138.31 seconds for a GCS motor score of 6 compared to a lower GCS motor score (95% CI -217.30, -59.32; $p < 0.001$). The number of lapses increased by 0.91 for a resuscitation performed during the weekend (95% CI 0.22, 1.59; $p < 0.01$), by 0.04 for each additional task related to oxygen delivery performed (95% CI 0.01,

0.08; $p < 0.01$), and by 0.62 for each instance of C-spine collar manipulation (95% CI 0.37, 0.87; $p < 0.001$).

Lapses in C-spine immobilization are frequent errors during pediatric trauma resuscitations. Most lapses are due to improper C-spine stabilization rather than a complete lack of stabilization. Tasks performed near the head and neck, including oxygen delivery and collar manipulation, have a high association with C-spine immobilization errors. These results suggest education focused on high-risk patient factors, resuscitation factors, and specific resuscitation tasks may reduce the likelihood of lapses in C-spine stabilization that occur during pediatric trauma resuscitation.

REFERENCES

1. Patel JC, Tepas III J, Mollitt DL, Pieper P. Pediatric cervical spine injuries: Defining the disease. *Journal of Pediatric Surgery*. 2001;36(2):373-376.
2. Jones TM, Anderson PA, Noonan KJ. Pediatric cervical spine trauma. *J Am Acad Orthop Surg*. 2011;19:600-611.
3. Webman RB, Fritzeen JL, Yang JW, et al. Classification and team response to nonroutine events occurring during pediatric trauma resuscitation. *Journal of Trauma and Acute Care Surgery*. 2016;81(4):666-673.

Resilience of Children with Chronic Health Conditions: The Impact of Neuropsychiatric Comorbidities

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Resilience, the ability to overcome adversity and effectively recover from stressful experiences, is a complex theory with many contributing factors. Previous studies have shown that condition-specific summer camps for children with chronic health conditions increase resiliency and adaptive coping skills, change attitudes toward the illness, and improve quality of life.^{1,2,3} Further research indicates that some modifiable resilience factors to improve children's health outcomes include fostering positive appraisal styles, bolstering executive function, and supporting maternal mental health.⁴ The aim of this study was to determine how neuropsychiatric comorbid diagnoses such as attention deficit hyperactivity disorder (ADHD), learning disability, and anxiety disorder influence the resilience of children with chronic health conditions.

Children with chronic health conditions including autism, epilepsy, cerebral palsy, Tourette's syndrome, sickle cell anemia, neurofibromatosis, congenital heart disease, and Type 1 diabetes attended Brainy Camps of Children's National Health System and participated in this study between 2010–16. Sixty-seven participants ages 7–17 completed the

Comorbidity (+/-)	Number of campers (n)	Pre-camp CD-RISC Score	Post-camp CD-RISC Score	Change in CD-RISC Score
ADHD (-)	35	68.09	78.36	+10.27
ADHD (+)	32	62.53	70.48	+7.95
Learning Disability (-)	30	71.63	79.24	+7.61
Learning Disability (+)	37	60.41	66.39	+5.98
Anxiety Disorder (-)	47	64.55	72.91	+8.36
Anxiety Disorder (+)	20	67.5	73.88	+6.38

FIGURE: Clinical factors noted around time of respiratory culture

Connor-Davidson Resilience Scale (CD-RISC) questionnaire pre- and post-camp. Parents of participants reported presence of comorbidities including ADHD, learning disability, and anxiety disorder. Averages for pre- and post-camp CD-RISC scores were taken for participants with ADHD, learning disability, or anxiety disorder, and were compared to scores for control participants without each comorbidity.

Averages for all groups indicated an increase in resilience scores. The increase was 10.27 points on the CD-RISC for the 35 participants without ADHD, and 7.95 points for the 32 participants with ADHD. The increase was 7.61 points for the 30 participants without learning disability, and 5.98 points for the 37 who had a learning disability. The increase was 8.36 points for the 47 participants without an anxiety disorder, and 6.38

points for the 20 with an anxiety disorder.

These findings demonstrated a positive shift in resilience for all participants with chronic health conditions who attended Brainy Camps.

... [M]odifications to the camp environment should be considered to further improve the camp's benefit for children with these neuropsychiatric comorbidities by better accommodating their unique needs.

However, the results indicated larger improvements in resilience for participants without comorbid diagnoses of ADHD, learning disability, or anxiety disorder. Therefore, modifications to the camp environment should be considered to further improve the camp's benefit for children with these neuropsychiatric comorbidities by better accommodating their unique

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needs. Some limitations of this study included small sample size as well as possible false reporting of comorbid diagnoses from parents. Further research is needed to understand how other factors, in addition to comorbidities, influence resilience of children with chronic health conditions, and how interventions such as residential

summer camps can also impact self-management and health outcomes.

REFERENCES

1. Cushner-Weinstein S, Berl M, Salpekar JA, et al. The benefits of a camp designed for children with epilepsy: evaluating adaptive behaviors over 3 years. *Epilepsy Behav.* 2007; 10: 170–8.
2. Briery BG, Rabian BJ. Psychosocial changes associated with participation in a pediatric summer camp. *Pediatr Psychol.* 1999; 24: 183–190.
3. Kiernan G, Gormaley M, and MacLachlan M. Outcomes associated with participation in a therapeutic recreation camping programme for children from 15 European countries: data from the “Barretstown Studies.” *Soc Sci Med.* 2004; 59: 903–913.
4. Traub F, Boynton-Jarrett R. Modifiable resilience factors to childhood adversity for clinical pediatric practice. *Pediatrics.* 2016; 10: 139(5).

Consistent Long-Term Therapy of Neovascular AMD Managed by 50 or More Anti-VEGF Injections Using a Treat-Extend-Stop Protocol

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Age-related macular degeneration (AMD) is a leading cause of vision loss in patients older than 65.¹ Neovascular AMD (nAMD) accounts for 10–15% of cases of AMD, and is responsible for more than 80% of severe vision loss and blindness attributable to AMD.² With the advent of intravitreal anti-VEGF agents, large randomized control trials (RCT) showed improvement in visual acuity (VA) at the one and two-year analysis. However, recent studies examining the long-term effectiveness of landmark trials have reported variable results.

For example, the Comparison of Age-related Macular Degeneration Treatments Trial, comparing ranibizumab or bevacizumab injected monthly or as needed (PRN),

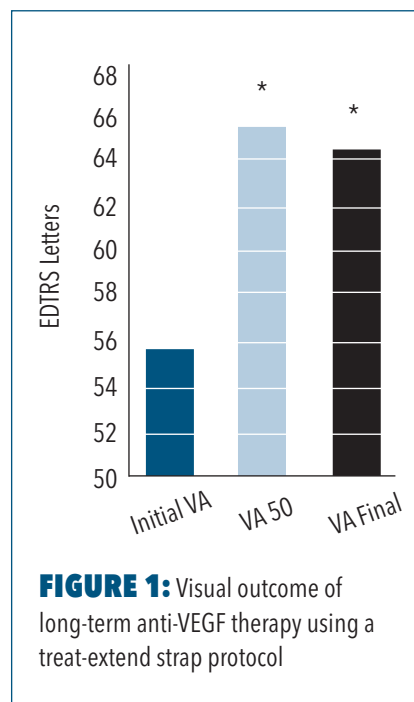


FIGURE 1: Visual outcome of long-term anti-VEGF therapy using a treat-extend strap protocol

demonstrated that treatments were effective through month 24; however, the five-year extended outcomes of this study, using a PRN method, demonstrated that VA gains were not maintained.³ Similarly, the seven-year outcomes of the SEVEN-UP study found an overall decline in vision using the PRN method.⁴

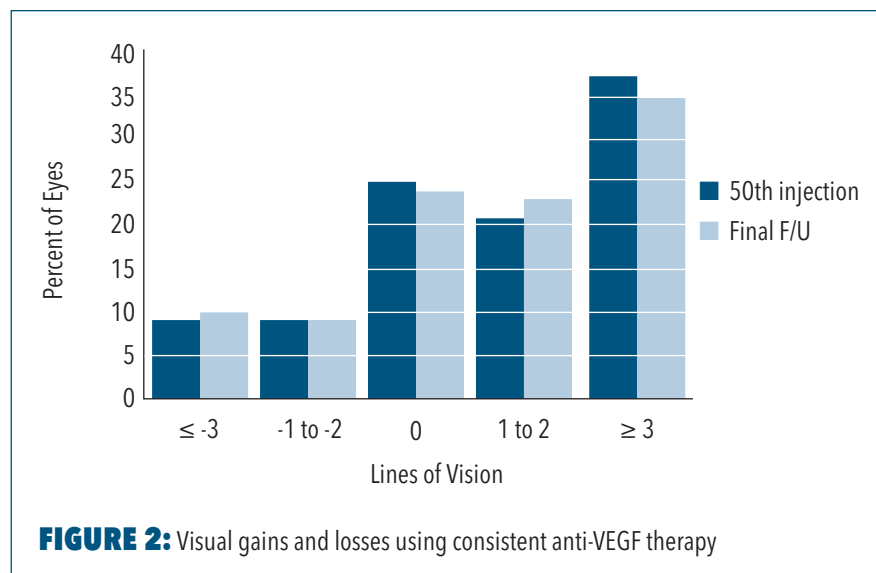
The purpose of this retrospective case study was to examine the clinical results and treatment patterns for patients with nAMD who were managed with a Treat-Extend-Stop (TES) protocol and received ≥50 injections of anti-VEGF agents.⁵

The clinical database of a retina-only practice was searched for patients who had a diagnosis of nAMD and were treated with anti-VEGF agents. A total of 996 patient records were examined between September 2005 and January 2017. Patients were included if they had received 50 or more intravitreal anti-VEGF injections. Participants underwent comprehensive ophthalmic examination, and were treated with anti-VEGF agents bevacizumab, ranibizumab or aflibercept as indicated. A TES treatment protocol was used, and at each visit patients also underwent clinical examination and relevant imaging studies, including BCVA vision (converted to ETDRS letters), optical coherence tomography and fluorescein angiography.

Continued on p. 33

Seventy-one eyes of 67 patients met the inclusion criteria. The participants were comprised of 41.8% males and 58.2% females, with an average age of 82.9 ± 6.2 years. Average time to the 50th injection was 77.4 months. Patients received an average of 63.7 injections over an average follow-up period of eight years. Prior to treatment, the mean VA was 55.6 ± 17.2 ETDRS letters (Figure 1). The mean initial vision was 20/80. After 50 injections, average VA was 65.3 ± 13.1 ETDRS letters (20/50) and the average change from baseline was 9.7 ± 19.6 ETDRS letters ($p < 0.001$). Visual improvement was maintained through final follow-up, with an average ETDRS letter score of 64.3 ± 14.6 ETDRS letters (20/50-), and an average change from baseline VA of 8.7 ± 20.2 ETDRS letters ($p < 0.001$). This was not significantly different compared to vision at the 50th injection ($p = 0.189$). Visual gains and losses were not significantly correlated with the type of anti-VEGF agent used ($p = 0.721$).

To our knowledge, our current study using a TES method is the longest to date, with an average follow-up time of eight years. The patients in this study, who received consistent long-term anti-VEGF treatment using a TES regimen, had an average



visual gain of +8.7 ETDRS letters, with only 9.9% of eyes losing more than 3 lines of VA. Moreover, 35.2% of subjects had a 3-line gain over the eight years (Figure 2) and an average vision of 20/50—overall—a figure that is reported by many RCTs within two years, but is later lost during extension studies. This study demonstrates that consistent long-term anti-VEGF treatment for nAMD is effective, safe, and can improve or maintain visual outcomes.

REFERENCES

1. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med*. 2008 Jun 12;358(24):2606-17.
2. Wong T, Chakravarthy U, Klein R, et al. The natural history and prognosis of neovascular age-related macular degeneration. A systematic review of the literature and meta-analysis. *Ophthalmology*. 2008;115:116-127.
3. Maguire MG, Martin DF, Ying GS, et al. Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016 Aug;123(8):1751-61.
4. Rofagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology*. 2013 Nov;120(11):2292-9.
5. Adrean SD, Chaili S, Grant S, et al. Recurrence Rate of Choroidal Neovascularization in Neovascular Age-Related Macular Degeneration Managed by a Treat and Extend Protocol. *Ophthalmology Retina*. 2017; Article in Press.

Association of Recently Described RANK and OPG Polymorphisms and Measures of Bone Quality in Young Adults

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Osteoporosis and resulting fragility fractures are a leading cause of disability, morbidity, and mortality in seniors. Increased fracture susceptibility is correlated with suboptimal bone quality measures, which are thought to be highly influenced by genetic factors. Roshandel et al¹ determined that specific receptor activator of nuclear factor-kappaB (RANK), RANK ligand (RANKL), and osteoprotegerin (OPG) single nucleotide polymorphisms (SNPs), previously identified by genome-wide association studies (GWAS), are associated with bone mineral density (BMD) and bone geometry parameters in older men. The RANK, RANKL, and OPG systems play a vital role in the regulation of osteoclasts and bone resorption.² Further investigation into genetic variation within these genes is essential in order to identify those at risk for future fragility fractures. Our study sought to expand the results of Roshandel et al,¹ which focused on the elderly, to determine whether RANKL/RANK/OPG SNPs rs3018362, rs17665435, rs6567276, and rs10505348 influence bone quality measures in younger populations.

The Assessing Inherited Markers

of Metabolic Syndrome in the Young (AIMMY) study comprised healthy, young adults (18–35 yrs) from the University of Calgary (UC) sub-cohort (n = 209). The Bone Health study comprised healthy African-American children (5–9 yrs, n = 97). The Functional Single Nucleotide Polymorphism Associated with Human Muscle Size and Strength (FAMuSS) study comprised healthy, young adults (18–40 yrs, n = 891). The bone quality phenotypes analyzed included total body BMD in AIMMY and total BMD adjusted for height in the Bone Health study measured by dual energy X-ray absorptiometry (DEXA). For FAMuSS, bone quality was analyzed from magnetic resonance images (MRIs) of the humerus and included polar moment of inertia, relative cortical volume, and robustness as described by Schlecht et al.³ Three SNPs for RANK (rs3018362, rs17665435, rs6567276) and one SNP for OPG (rs10505348) were genotyped in the AIMMY sub-cohort using ThermoFisher's Applied Biosystems Taqman SNP genotyping assays. Amplified DNA samples were analyzed and alleles were determined through allelic discrimination assays using Applied Biosystems's 7900HT Real-Time PCR machine. SNPs were genotyped in the FAMuSS cohort using Illumina Multi-Ethnic Genotyping Array (MEGA). Hardy-Weinberg equilibrium was tested for the allelic frequency of each SNP. All outcomes were adjusted for age, and analysis of covariance (ANCOVA) was used to test for associations.

Our results did not support those of Roshandel et al¹ and suggested that the SNPs rs10505348, rs3018362,

rs17665435, and rs6567276 were not associated with BMD or any other bone quality measures in young adults. We suspect that the lack of association in our study indicates these SNPs may not play a role in the development of peak bone mass despite being important in determining bone quality in seniors. The only association that approached significance was rs3018362 and height-adjusted BMD in males in the Bone Health cohort (p = 0.07). Our study faced some limitations that could have accounted for the lack of associations. The RANKL/RANK/OPG signaling pathway represents just a single mechanism in the multifactorial regulation of bone quality. To further characterize the effect of RANKL/RANK/OPG variations on bone quality phenotypes, future studies should evaluate the relationship between these variants and bone phenotypes in cohorts of different ages and ethnicities. In addition, expanding the bone quality phenotypes analyzed to include peripheral quantitative computed tomography measures would provide more insight into the extent of influence that these variants have.

REFERENCES

1. Roshandel D, Holliday KL, Pye SR, et al. Influence of polymorphisms in the RANKL/RANK/OPG signaling pathway on volumetric bone mineral density and bone geometry at the forearm in men. *Calcif Tissue Int*. 2011;89:446–55.
2. Boyce BF, Xing L. Biology of RANK, RANKL, and osteoprotegerin. *Arthritis Res Ther*. 2007;9(Suppl 1):S1.
3. Schlecht SH, Bigelow EMR, Jepsen KJ. How does bone strength compare across sex, site, and ethnicity? *Clin Orthop Relat Res*. 2015;473:2540–7.

Cochlear Implantation in a Patient with Early Cochlear Sclerosis due to Sickle Cell Disease

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Sickle cell disease (SCD) is an inherited disorder of red blood cells. Patients with SCD suffer end-organ damage due to vascular occlusion of small vessels during a sickle cell crisis. Homozygous SCD patients tend to have much higher incidence of sensorineural hearing loss (SNHL) compared to the general population. The incidence of SNHL in patients with SCD reaches 29% in developing nations and around 12% in the United States.¹

Despite a high prevalence of SNHL in patients with SCD, only five cochlear implantation surgeries have been reported in this population,²⁻⁵ four of which were caused by the SCD.²⁻⁴ All but one patient had normal cochleae. The exception was a case of partial cochlear ossification, which required the insertion of the electrode into the scala vestibuli.³

We report a clinical case of a patient with SCD who developed bilateral profound SNHL sequentially within one year with signs of early cochlear duct obliteration found during cochlear implantation.

A 19-year-old female patient with SCD who had suffered multiple

episodes of crisis developed severe to profound SNHL in her left ear precipitated by an acute ear infection. Three months later she developed severe to profound SNHL in her right ear preceded by an acute sickle cell crisis following a urinary tract infection. The patient also complained

of disequilibrium and bilateral non-pulsatile tinnitus.

Magnetic resonance imaging (MRI) of the brain showed signs of subacute bilateral labyrinthitis as evident by the absence of normal fluid

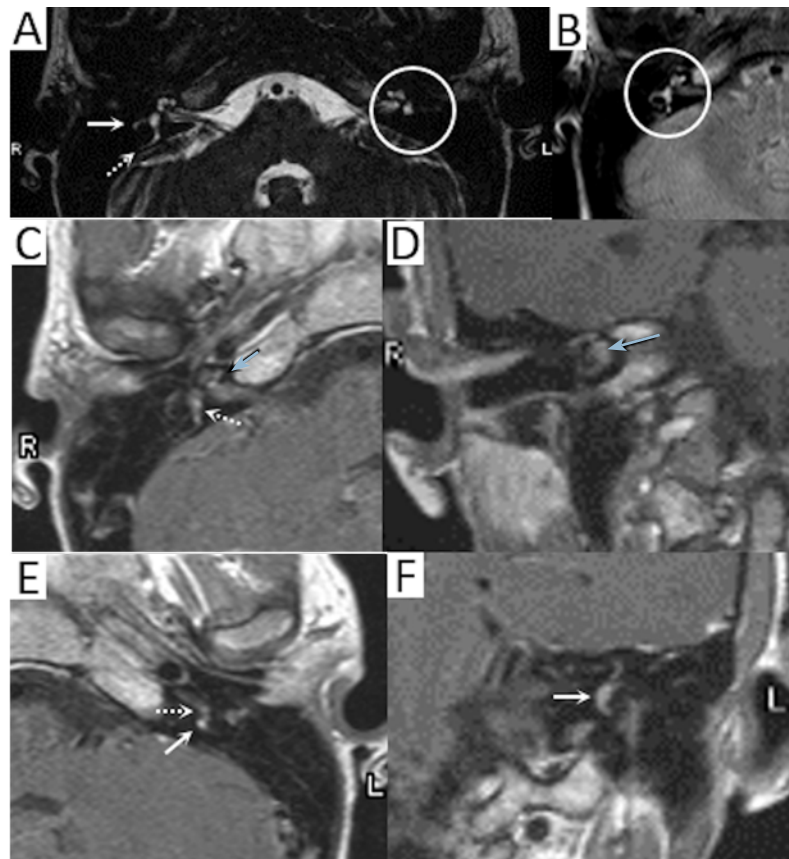


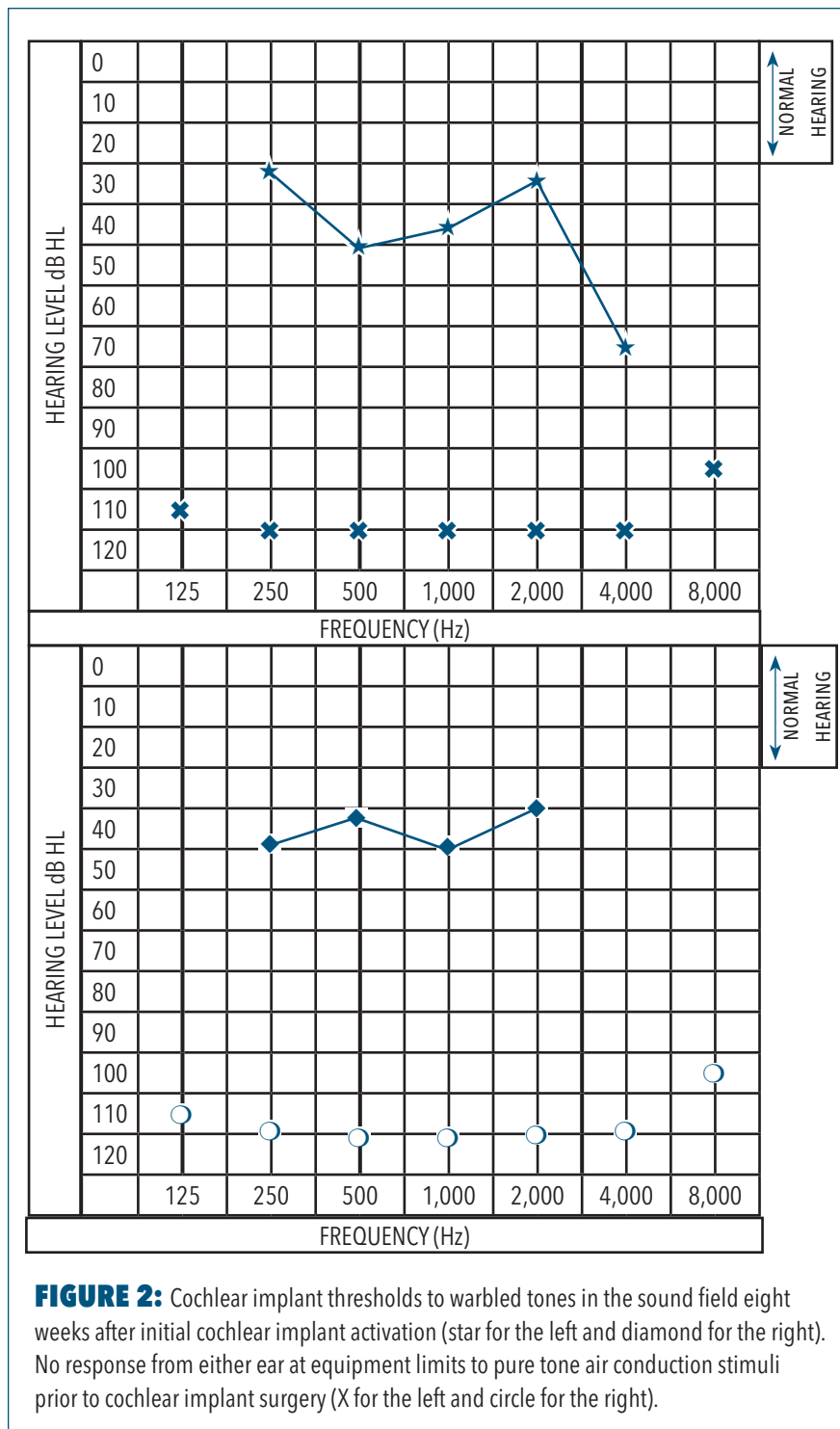
FIGURE 1: (A) Axial volumetric T2-weighted image (FIESTA) at the level of the internal auditory canal (IAC) shows normal fluid signal in the visualized portion of the right lateral (solid arrow) and posterior (dashed arrow) semicircular canals. In the corresponding portion of the left temporal bone (solid circle), the fluid signal in these structures is absent. (B) Axial fluid attenuation inversion recovery (FLAIR) shows abnormal bright signal in the right labyrinthine structures (solid circle), consistent with increased protein content. Axial (C) and coronal (D) T1-weighted images through the right labyrinthine structures after the administration of contrast show patchy enhancement of the cochlea (blue arrow) and vestibule (dashed arrow). Axial (E) and coronal (F) T1-weighted images through the left labyrinthine structures after the administration of contrast shows patchy enhancement of the vestibule (solid arrow) and to a lesser degree within the cochlea (dashed arrow).

Continued on p. 36

signal on T2-weighted images, elevated protein content seen as abnormally bright signal in fluid-attenuated inversion recovery (FLAIR) images, as well as patchy enhancement of these structures after administration of contrast (Figure 1).

The patient received bilateral cochlear implantation with Med-El Synchrony Flex 28 electrodes. Prior to surgery, the patient underwent exchange transfusion to prevent vaso-occlusive crisis. We found pneumatized normal mastoids bilaterally with a small amount of inflammatory tissue in the facial recess and middle ear. The hook region of the cochlea was partially obliterated bilaterally and gentle serial dilations with insertion guides were required for complete electrode insertion. Intraoperative telemetry measurements revealed low impedance and adequate auditory nerve response thresholds. A sound field audiogram eight weeks after initial activation demonstrated thresholds ranging from 25 dB to 50 dB hearing level (HL) compared to profound hearing loss preoperatively (Figure 2).

The cochlea is supplied by the terminal cochlear branch of the labyrinthine artery, a branch of the anterior inferior cerebellar artery.³ Having a solitary terminal blood supply makes the cochlea quite vulnerable to vascular occlusion caused by sickled red blood cells during sickle cell crises. Also, transient occlusion of the anterior inferior cerebellar artery may lead to altered hemodynamics and reperfusion injury, which may cause labyrinthine hemorrhage. This phenomenon is theorized to incite reparative response that cascades from fibrosis to sclerosis to ossification of the inner ear structures.



Considering the high incidence of SNHL in SCD patients, screening audiograms and education of parents and primary physicians in the urgency of SNHL is important. As we currently do not possess adequate treatment for cochlear infarction or hemorrhage

in these patients, cochlear implantation remains the treatment of choice. Expedited cochlear implantation may provide more satisfactory results as cochlear fibrosis tends to happen quickly in these patients.

REFERENCES

1. Ajulo SO, Osiname AI, Myatt HM. Sensorineural hearing loss in sickle cell anaemia: A United Kingdom study. *J Laryngol Otol.* 1993;107:790-4.
2. Mace AD, Ferguson MS, Offer M, et al. Bilateral profound sudden sensorineural hearing loss presenting a diagnostic conundrum in a child with sickle cell anemia. *J Laryngol Otol.* 2009;123:811-6.
3. Ashfield T, Pai I, Wilson K, et al. Cochlear implantation in children with sickle cell disease. *Pediatr Int.* 2015;57:174-6.
4. Almuhawes FA, Hagr AA. Cochlear implant for bilateral profound sensorineural hearing loss in an adolescent with sickle cell anemia. *Ann Saudi Med.* 2014;34:167-70.
5. Tang S, Nickel C, Lalwani AK. Pulmonary embolism and infarct after bilateral cochlear implantation in a patient with newly diagnosed sickle/β+ thalassemia. *Otol Neurotol.* 2015;36:1463-6.

Class 1-Selective Histone Deacetylase Inhibitors Promote HIV Latency-Reversal and Clearance

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Latent human immunodeficiency virus (HIV) infection within long-lived cells establishes a persistent reservoir that is a major barrier to cure. Pharmacologic reversal of HIV latency has been proposed as a mechanism to promote cytotoxic active infection and the elimination of persistent viral reservoirs. Using in vitro models of HIV latency, combinations of transcription factor activating agents with histone deacetylase inhibitors (HDIs) have been shown to synergistically reverse HIV latency. However, these results have not translated into positive effects in in vivo or in ex vivo experiments using HIV-infected patient-derived CD4⁺ T-cells.¹⁻⁴ Importantly, HDIs that affect a broad range of isoforms of histone deacetylases (pan-HDIs) have been the focus of most of these

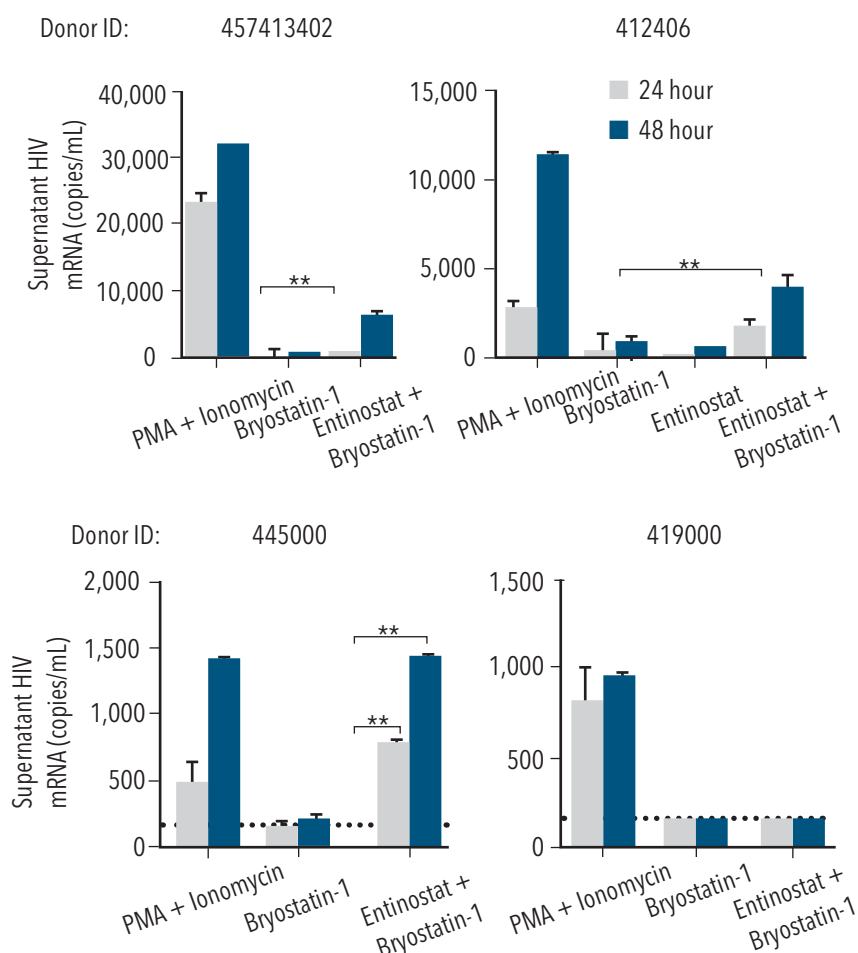


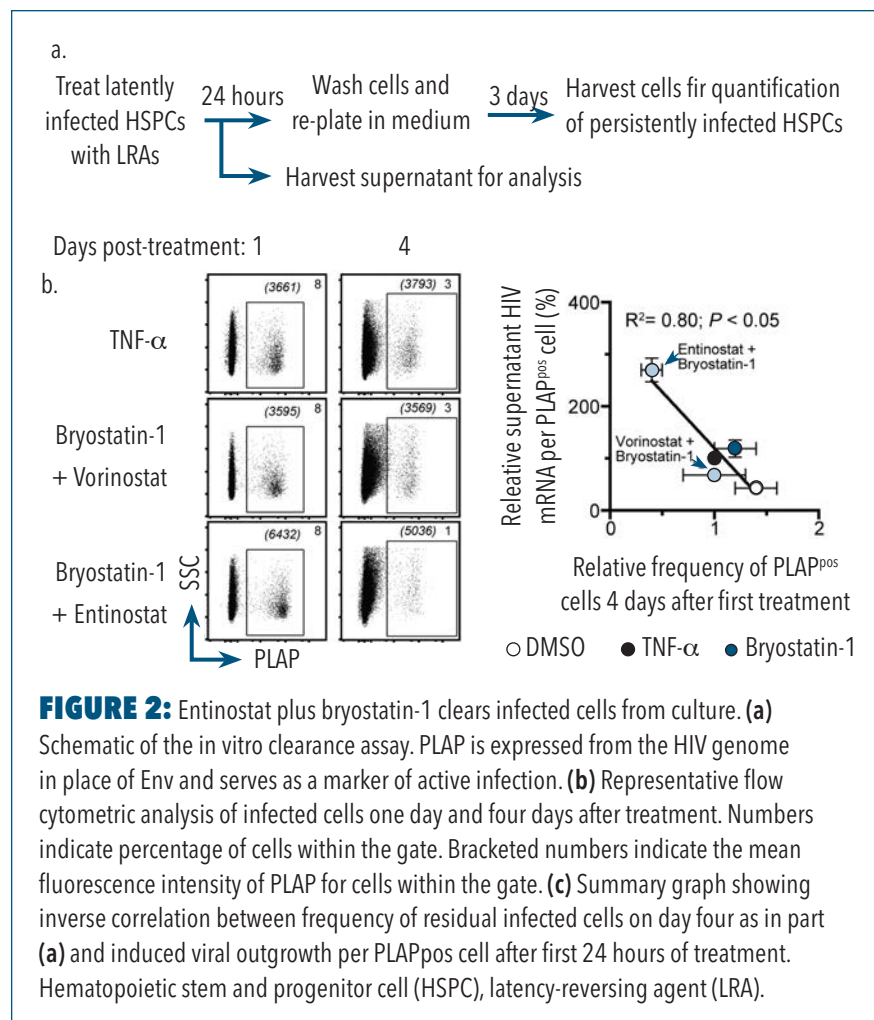
FIGURE 1: Entinostat plus bryostatins-1 induces maximum viral outgrowth in latently infected CD4⁺ T-cells from HIV-infected individuals. HIV viral outgrowth from patient-derived CD4⁺ T lymphocytes treated with indicated drugs (mean ± standard deviation of experimental duplicates). Limit of quantification is indicated by the dotted horizontal line. P values were calculated by unpaired student's t-tests. ** p < 0.01.

Continued on p. 38

studies, despite the knowledge that HIV latency is only affected by class I histone deacetylases.⁵ Therefore, we hypothesized that the combination of the class I-selective HDI entinostat plus the NF- κ B agonist bryostatin-1 would maximally reverse HIV latency from CD4⁺ T-cells from HIV-infected donors and reduce the latent viral reservoir.

When we treated CD4⁺ T-cells from HIV-infected people, we detected virus outgrowth at 24 and 48 hours with bryostatin-1 alone in three of four donors. Remarkably, we detected significantly more virus outgrowth with the combination of bryostatin-1 plus entinostat (Figure 1; 5- to 11-fold). Concomitant with increased virion release, we also detected more cell-associated HIV mRNA when cells were treated with bryostatin-1 plus entinostat compared to bryostatin-1 alone in all four donors (data not shown). Collectively, these data are the first example of any HDI enhancing virus outgrowth from patient samples.

To test the effect of treatment conditions on the elimination of latent viral reservoirs, we developed a novel primary human hematopoietic stem and progenitor cell HIV latency model system (Figure 2a). Using this system, we quantified the potency of induced HIV latency-reversal (supernatant HIV mRNA) and the frequency of infected cells that emerged one day after treatment and remained after three days in culture without any stimulus. One day post-treatment, the frequency of induced PLAP^{pos} cells was similar among all conditions tested except for our negative DMSO control (Figure 2b). Consistent with previous work,² HIV protein production was most potently induced by the combination of entinostat plus



bryostatin-1 as measured by PLAP mean fluorescence intensity (MFI) (Figure 2b). Interestingly, it was only this combination of entinostat plus bryostatin-1 that then reduced the frequency of residual infected cells in culture four days post-treatment (Figure 1b). Finally, we demonstrated a strong inverse correlation between the potency of induced viral outgrowth from latently infected cells (supernatant HIV mRNA) and the frequency of residual actively infected cells in culture four days after treatment (Figure 1c).

In summary, our results demonstrate that the combination of the class I-selective HDI entinostat plus bryostatin-1 maximally reverses HIV latency and promotes reservoir elimination. We have also shown that

pan-HDIs limit potent HIV latency-reversal due to inhibition of important proviral factors (Hsp90 and NF- κ B) affected by the activity of non-class I histone deacetylases (data not shown). Therefore, this supports the rationale of the development of a more targeted latency-reversal regimen that avoids nonspecific/off-target effects, advances the field toward the goal of eliminating the viral reservoir in HIV-infected people, and contributes to a cure.

REFERENCES

1. Bullen CK, Laird GM, Durand CM, et al. New ex vivo approaches distinguish effective and ineffective single agents for reversing HIV-1 latency in vivo. *Nat Med.* 2014;20:435-9.

Continued from p. 38

2. Albert BJ, Niu A, Ramani R, et al. Combinations of isoform-targeted histone deacetylase inhibitors and bryostatins analogues display remarkable potency to activate latent HIV without global T-cell activation. *Sci Rep.* 2017;7:7456.
3. Rasmussen TA, Tolstrup M, Brinkmann CR, et al. Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial. *Lancet HIV.* 2014;1:e13-21.
4. Archin NM, Bateson R, Tripathy MK, et al. HIV-1 expression within resting CD4+ T cells after multiple doses of vorinostat. *J Infect Dis.* 2014;210:728-35.
5. Keedy KS, Archin NM, Gates AT, et al. A limited group of class I histone deacetylases acts to repress human immunodeficiency virus type 1 expression. *J Virol.* 2009;83:4749-56.

Impact of Polymorphisms in PTK2 on Intrinsic Muscle Strength

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Recent studies have begun to search for correlations between genetic variations and muscle strength. One such study, by Stebbings et al.¹, examined two single nucleotide polymorphisms (SNPs) — rs7843014 and rs7460 — on the PTK2 gene. The study found that genetic variation in the PTK2 gene impacts muscle-specific force, which is measured as force generated per unit of cross-sectional area of muscle. PTK2 is responsible for costamere formation and turnover in striated muscles. Costameres function to attach the Z-line to the sarcolemma and in turn regulate the amount of muscle-specific force a muscle can exert. Muscle-specific force ultimately represents the intrinsic strength of a muscle and is a key determinant of functional capacity and mobility. This study sought to expand on prior research by looking for associations between genetic variants of PTK2 and

measures of grip strength, as well as general anthropomorphic measures, in a cohort of healthy young adults.

Our study used the Assessing Inherited Markers of Metabolic Syndrome in the Young (AIMMY) University of Calgary subset consisting of 190 healthy, primarily Caucasian individuals between the ages of 18 and 35. We assessed their phenotypes for height, weight, VO₂ max, max grip strength, and body mass index (BMI). DNA samples from these patients were genotyped using ThermoFisher Taqman SNP genotype assays. After completion, the samples underwent the Applied Biosystems 7900HT real-time polymerase chain reaction (PCR) process. Analysis of covariance (ANCOVA) models were then used to perform statistical analysis to look for genotype-phenotype associations and ensure Hardy-Weinberg equilibrium.

Unlike the findings by Stebbings et al.,¹ we did not find an association between the PTK2 genotypes and grip strength. This may indicate that grip strength and muscle-specific force do not measure similar parameters of muscle strength. Stebbings et al.¹ used a leg press to measure the muscle-specific force of the quadriceps, while a hand strength dynamometer was used to assess grip strength in the AIMMY cohort. Although both

are pennate muscles, the hand muscles pale in comparison to the quadriceps, which are the largest muscle groups in the body. It has been found that larger muscles generate proportionally greater amounts of force, so the difference could be related to a lower statistical power in the grip strength test. Genetic variation in PTK2 has also been previously associated with VO₂ max, but no association was found in the current study.

Interestingly, positive associations were found between genetic variants rs7843014 and rs7460 in PTK2 and BMI, although not found in previous studies.^{1,2} Individuals with high levels of functioning PTK2 have been found to have increased strength due to increased costamere density. A higher costamere density equates to more muscle myofibrils, which results in larger and presumably heavier muscles. This finding was sexually dimorphic and only observed in males. This could be attributed to differential acquisition and maintenance of muscle mass based on sex. There was also an association between genetic variant rs7843014 and height in males.

We identified a potentially novel association between genetic variants in PTK2 and anthropomorphic phenotypes, specifically BMI and height.

Continued on p. 40

Continued from p. 39

However, we were unable to confirm the effects of genetic variants on measures of intrinsic muscle strength, namely max grip strength or VO₂ max in terms of functional capacity.

Further research is needed to confirm this newly identified role for PTK2.

REFERENCES

1. Stebbings G, Williams A, Day S, et al. Polymorphisms in PTK2 are associated with skeletal muscle specific force: An independent replication study. *Eur J Appl Physiol*. 2017;117:713-20.

2. Erskine R, Williams A, Jones D, et al. Do PTK2 gene polymorphisms contribute to the interindividual variability in muscle strength and the response to resistance training? A preliminary report. *J Appl Physiol*. 2012;112:1329-34.

Medical Education:

Developing a Curriculum for Fourth-Year Medical Students Emphasizing Social Justice, Cultural Competency, Cost Consciousness, and Developing Students into Educators

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Providers are inevitably faced with treating economically disadvantaged and culturally diverse populations. To meet the needs of socially complex patients, further training is warranted. One way of addressing this need is through service learning, defined as active community engagement with ongoing student reflection.¹ Students that engage in service learning are

better prepared to treat vulnerable patients than students in a conventional curriculum.² Furthermore, physicians are also expected to engage

in educating their peers, but with little guidance or preparation.³

The course objectives and requirements are listed below organized by theme:
Table: Course requirements

Course Theme	Learning Objectives	Requirements
Service learning & Social Justice	1) Manage complex primary care patients in low resource setting.	- Clinical encounters* - Note writing - Lab follow-up & patient care coordination
	2) Recognize the distinct care delivery models that form a safety net within the metro DC area.	- Clinical encounters - Evening site visit to local community organization
	3) Recognize the role social determinants of health (SDOH), social justice, and institutional racism play in health outcomes and disparities.	- Clinical encounters - Group reflection
Cultural Competency	4) Understand and reflect on cultural competency in the clinical setting.	- Case reports* - Group reflection
Cost Conscious Care	5) Analyze the delivery of cost-conscious care.	- Case reports - Practice cost-consciousness care during clinical encounters - Group reflection
Developing students into educators	6) Demonstrate ability to act as preceptor in the clinical setting and develop skills as an educator.	- Preceptor for first year medical students in clinic - Teaching rounds*

*Clinical encounters: Students are required to complete 12 clinic shifts at GWU's Healing Clinic.

*Case reports: Students are required to submit 2 case reports; one case report with emphasis on social history and cultural context of the patient, and the other on cost analysis of the visit.

*Teaching rounds: students are required to prepare 1 teaching rounds presentation on a topic of their choice, which they will present to first and second year students.

Continued from p. 40

We aim to address these needs by expanding an existing Community Health Care elective at George Washington University's (GW) free student-run Healing Clinic. We are developing a curriculum that is founded in service learning with a particular emphasis on cultural competency, cost-conscious care, and developing students into educators.

In addition to group reflection, surveys will be distributed to students in the elective assessing several aspects, including, but not limited

to: satisfaction with the elective, confidence in the preceptor role, confidence in balancing cost with quality care, understanding of SDOH, and impact on future practice.

As young providers entering the field, we will be faced with serving a complex and diverse patient population. Community engagement is one important way to better prepare providers. Through the proposed curriculum, we hope to further prepare our peers and ourselves to promote health equity. Data from the surveys will be evaluated throughout the year.

REFERENCES

1. Deans T. Service-learning in two keys: Paulo Freire's critical pedagogy in relation to John Dewey's pragmatism. *Mich J Community Serv Learn*. 1999;15-29.
2. Reeve C, et al. The impact of socially-accountable health professional education: A systematic review of the literature. *Medical Teacher*. 2017;39:1, 67-73.
3. Jewett, et al. Teaching Residents How to Teach: A One-Year Study. *Journal of Medical Education* 1982;57, 361-366.
4. Bardach, et al. Teaching to teach: enhancing fourth year medical students' teaching skills. *Med Education*. 1996;37:1031-1032.
5. Bing-You, Sproul. Medical students' perceptions of themselves and residents as teachers. *Med Teach*. 1992 14:133-138.

Enriching the Medical Student Radiology Clerkship: Simulating the Radiologist's Experience

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Current radiology training in medical schools is still predominantly limited to passively observing the radiologist at the workstation and through lectures, textbooks, and online sources. Evaluation is also mainly limited on still image interpretation or knowledge-based multiple-choice questions.¹ In order to create a tailored and active learning experience, and to evaluate students' ability in image interpretation, we utilized an open-source web-based Picture Archiving and Communication System (PACS) named "Weasis" with our own reporting system.^{2,3}



FIGURE 1: Weasis interface accessed using hospital computer screenshot. Using browser to serve as a DICOM viewer without special software required, and all functions (window width and level, zoom, measurement, etc.).

Attending radiologists can send desired anonymized studies from hospital PACS during read-out to a shared secure server on the hospital network. Cases can be immediately

accessed by trainees on any computer connected to the shared network. Students, simultaneously, can

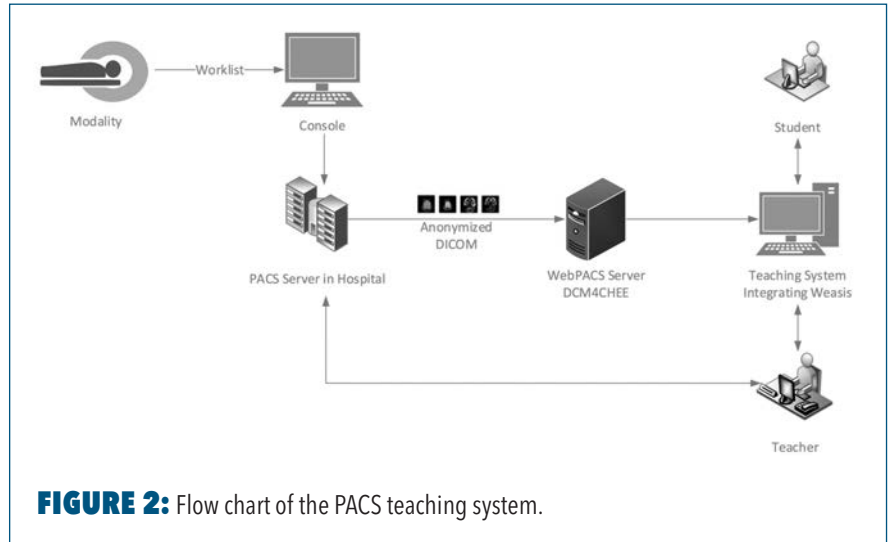
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simulate being a radiologist and independently formulate an opinion and write up a brief report, without the need for occupying an expensive PACS workstation. Trainees can access a list of cases to create a very short report for each case, which can later be reviewed by a resident or an attending radiologist. This can be used for examination purposes, both for radiology rotation evaluation of medical students and as part of the pre-call Objective Structured Clinical Examinations of first-year residents.

We established a new PACS teaching system by utilizing the open-source PACS system “dcm4chee” and integrating Weasis as an imaging viewing browser, MySQL as a database, and JBOSS as an application server. The developmental environment is MyEclipse, and the developmental language is JAVA. We used WADO (Web Access to Digital Imaging and Communications in Medicine (DICOM) Object) to achieve web-client DICOM image access.² Java applets are used via a browser to serve as a DICOM viewer without special software required, and all functions (window width and level, zoom, measurement, etc.) are provided as

controls within the server application.³ However, Weasis does not come with a reporting system, so we built one using the same methodology for student reporting and preceptor commenting and grading.

By implementing Weasis and the add-on reporting system, a real-time, easy-access, sophisticated Image Database can be established. The content of examination will be more versatile and similar to clinical scenarios. Therefore, this implementation provides a new opportunity for both training and evaluation purposes for radiology programs.



REFERENCES

1. McEvoy FJ, Shen NW, Nielsen DH, Buelund LE, Holm P. Online Radiology Reporting with Peer Review as a Learning and Feedback Tool in Radiology; Implementation, Validity, and Student Impressions. *Journal of Digital Imaging*, 30. 2017;(1), 78-85.
2. Warnock, MJ, Toland, C, Evans, D, Wallace, B, & Nagy, P. Benefits of using the DCM4CHE DICOM archive. *Journal of Digital Imaging*, 20. 2017;(1), 125-129.
3. Koutelakis GV, Lympelopoulous DK. PACS through web compatible with DICOM standard and WADO service: advantages and implementation. In *Engineering in Medicine and Biology Society*, 2006. EMBS '06. 28th Annual International Conference of the IEEE (pp. 2601-2605). IEEE.

Comparison of HCV-Related Diagnoses, Liver Scores, and Mortality in Patients Based on HIV Status Between 2008–15 at DC-VAMC

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Chronic hepatitis C virus (HCV) infection is a prevalent disease among veterans with a rate 2–3-fold higher than that of the general population within the United States.¹ Co-infection with HCV has been estimated in nearly 40% of HIV-infected veterans.² Recent advancements in HCV treatment have resulted in a shift from pegylated interferon-based regimens to the use of directly acting agents (DAA).³ The goal of HCV treatment is to achieve sustained virologic response (SVR), which has been associated with lower rates of end-stage liver disease, hepatocellular carcinoma, and death.⁴ From prior studies on HCV infection in the general population, pegylated interferon-based regimens resulted in SVR rates of 41% among HCV mono-infected patients and 27% among HCV/HIV co-infected patients.⁵ However, approximately 90% of all patients have attained SVR after DAA treatment.⁴

At the Washington DC VA Medical Center (DC-VAMC), pegylated interferon-based regimens were used to treat HCV infection

Hepatitis C parameters		All HCV Patients	HCV Mono-Infection	HCV/HIV Co-Infection	p-Value
Total		5,114	4,690	424	
Associated Diagnosis	Cirrhosis without mention of alcohol	1,012 (20%)	938 (20%)	74 (17%)	0.2313 ²
	Primary malignant neoplasm of liver	240 (5%)	230 (5%)	10 (2%)	0.0158 ¹
Liver Scores	APRI>1.5	628/4,896 (13%)	569/4,480 (13%)	59/416 (14%)	0.4307 ²
	FIB-4>3.25	1,244/4,896 (25%)	1,113/4,480 (25%)	131/416 (31%)	0.0035 ²
	MELD>30	100/4,524 (2%)	89/4,134 (2%)	11/390 (3%)	0.3674 ¹
	MELD-Na>30	150/4,524 (3%)	134/4,134 (3%)	16/390 (4%)	0.3729 ¹
All-Cause Mortality					
2008–15		934 (18%)	850 (18%)	84 (20%)	0.4262 ²

TABLE: Summary of Hepatitis C (HCV) parameters and clinical outcomes where numbers (% of group total) for all HCV patients between 2008–15 (¹Two-tailed Fisher's Exact Test, ²Two-tailed Chi-square test with Yate's correction)

during 2008–13, and DAAs became the preferred treatment in 2014–15. We describe HCV-related diagnoses, calculated liver scores, and mortality for our patients during 2008–15 at the DC-VAMC in the Table.

Among all patients, 20% had the diagnosis of cirrhosis without mention of alcohol by ICD-9 code 571.5 with no significant difference between the proportions of mono- and co-infected patients with cirrhosis. Among all patients, 5% had the diagnosis of primary malignant neoplasm of the liver by ICD-9 code 155.0, with a significantly greater proportion of HCV mono-infected patients

having hepatocellular carcinoma than HCV/HIV co-infected patients (5% vs. 2%, $p=0.0158$ by 2-tailed Fisher's exact test). For calculated liver scores, a significantly greater proportion of HCV/HIV co-infected patients had Fibrosis-4 (FIB-4) >3.25 compared to HCV mono-infected patients (31% vs. 25%, $p=0.0035$ by 2-tailed Chi-square with Yate's correction). However, similar proportions of mono and co-infected patients had AST to Platelet Ratio Index (APRI)>1.5 (13% vs. 14%, $p=0.4307$ by 2-tailed Chi-square with Yate's correction), MELD score

Continued on p. 44

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>30 (2% vs. 3%, $p=0.3674$ by 2-tailed Fisher's exact test), and MELD-Na score >30 (3% vs. 4%, $p=0.3729$ by 2-tailed Fisher's exact test). There were no differences in all-cause mortality between mono- and co-infected patients (18% vs. 20%, $p=0.426$ by 2-tailed Chi-square with Yate's correction) annually and during our entire study period.

We found a significantly higher proportion of HCV mono-infected patients with a diagnosis of hepatocellular carcinoma compared to co-infected patients. This outcome may reflect differences in patient populations, as our HCV/HIV co-infected patients were predominantly

men with high CD4 counts >400 cells/mm³. In addition, our patients' HIV infections were fairly well controlled, with 78% achieving HIV suppression on antiretroviral therapy during the study period. Although FIB-4 was the only significantly different liver score, suggesting a greater proportion of co-infected patients had advanced hepatic fibrosis or cirrhosis, FIB-4 has been viewed as a better predictor for the clinical outcomes of hepatic decompensation, hepatocellular carcinoma, and mortality compared to Child-Turcotte-Pugh and MELD scores.⁴ Nevertheless, there were no differences between our two groups for the diagnosis of cirrhosis without mention of alcohol and all-cause mortality during the study period.

REFERENCES

1. Beste LA, Ionnaou GN. Prevalence and Treatment of Chronic Hepatitis C Virus Infection in the U.S. Department of Veterans Affairs. *Epidemiologic Reviews*. 2015;37(1):131-143.
2. Fischer MJ, Wyatt CM, Gordan K, et al. Hepatitis C and the Risk of Kidney Disease and Mortality in Veterans with HIV. *Journal of Acquired Immune Deficiency Syndromes*. 2010; 53(2):222-226.
3. Bertino G, Ardiri A, Proiti M, et al. Chronic hepatitis C: This and the new era of treatment. *World J Hepatol*. 2016;8(2):92-106.
4. Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfecting with HIV/HCV. *JAMA*. 2012;308 (4):370-378.
5. Graham CS. Hepatitis C and HIV Co-infection: Closing the Gaps. *JAMA*. 2015;313(12):1217-1218.

The Impact of Changing Scope of Practice Laws on Nurse Practitioner Billing Patterns

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Over the last few decades, scope-of-practice laws for nurse practitioners (NPs) have changed rapidly, allowing for increased practice and prescribing autonomy in the hopes that these providers can help alleviate some of the workforce shortages in primary care that exist all over the United States. Despite this trend toward enhanced autonomy, scope-of-practice laws vary widely by state, this includes rates of reimbursement to

NPs paid for by Medicaid, with some states reimbursing NPs at 100% of the physician rate and others only reimbursing at 75% of the physician rate.¹ At the federal level, Medicare implemented legislation in 1998 that began reimbursing NPs at a rate of 85% of a physician's fee regardless of site of practice or geographic location, a change from previous versions that restricted NP reimbursement to rural areas and sites specific to long-term or follow-up care.² Since then, the number of NPs who have been billing on their own has been increasing over time. The current study examined whether a change in scope-of-practice law toward a more autonomous practice changed the rate at which NPs billed independently for their services.

This project used a 5% sample of Medicare claims data from 1999

to 2014 to track the pattern in the number of NPs who were billing Medicare for their services. In order to bill Medicare as an independent provider, NPs would need to have their own National Provider Identifier (NPI). Unique NPI numbers were totaled and plotted over time by the state to evaluate the change in trends. State changes to NP laws were identified and catalogued through use of West Law, a legal research service that archives state legislative and regulatory changes. After identifying all relevant changes to scope-of-practice laws for NPs by state, NP billing trends were evaluated at times before and after these had gone into effect.

Changes in scope-of-practice laws for NPs did not change the trends in the number or rate of these providers

Continued on p. 45

billing for their services. The number of NPs billing independently for Medicare had been increasing steadily over time. In a given state, a change toward more autonomy in practice did not affect the rate of the increase. The same trend was also seen in states that had the most dramatic changes in their laws. Examples of this can be seen in Figure 1. In 2005 in Wyoming and 2010 in Maryland, each state passed legislation removing the requirement for NPs to have a collaborative agreement with a physician, effectively allowing for independent practice. Yet, the figures show the trends in NPs billing independently was consistent with rates seen before these legislative changes.

Understanding the effect of changing scope-of-practice laws on NP practice patterns will be essential to informing current and future regulation of these providers. While this trend has been increasing steadily over time, the rate at which NPs billed Medicare independently did not dramatically change with increased practice and prescribing autonomy in state legislation, which may be a key piece to alleviating some of the strain on the primary care workforce.

REFERENCES

1. Kaiser Family Foundation. Medicaid Benefits: Nurse Practitioner Services, 2003–12. (Accessed Sept. 15, 2017, at <https://www.kff.org/medicaid/state-indicator/nurse-practitioner-services>)
2. American Association of Nurse Practitioners Fact Sheet: Medicare Reimbursement, 2013. (Accessed Sept. 15, 2017, at <https://www.aanp.org/practice/business-practice-management/reimbursement/68-articles/325-medicare-reimbursement>)

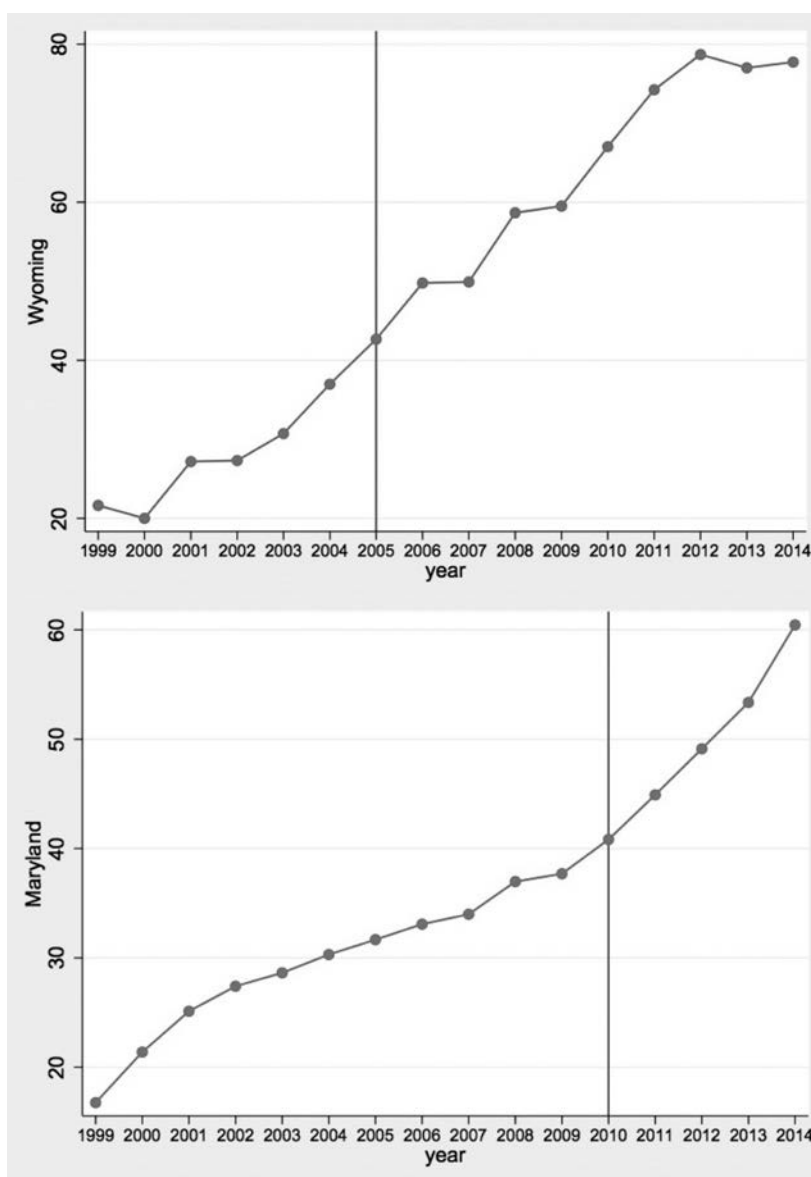


FIGURE: Trends in nurse practitioner independent Medicare billing rates, Wyoming and Maryland, 1999–2014

How the European Union Is Embracing Cross-Border Telemedicine and What the U.S. State Medical Boards Can Learn From It

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Despite the many advances in the field of telemedicine, U.S. state and federal laws have not kept pace with these technological advancements and may operate as a barrier to growth in the field. On the other hand, the European Union has developed a robust legal framework for the practice of telemedicine. The aim of this research project is to evaluate what elements of the EU legal experience could be used to support efforts to better align telemedicine law with the practice of telemedicine in the United States.

Based on the 2015 EU Guidelines, by 2020, a French physician may be able to see a German patient online and have instant access to the patient's medical record, automatically translated into the French language.¹ The EU has prioritized the creation of a legal framework that fully supports cross-border telemedicine.² As early as 2000, the EU broadened medical licensure requirements

	United States	Europe
Medical License Requirements for Crossborder Telemedicine	Most states require a medical license for both the state where patient is located and the state where physician is practicing Interstate Medical Licensure Compact: Expedited multistate license process, available in 12 states	License required in nation where physician is located without regard to patient location EU eCommerce Directive of 2000 established that a EU physician is required to be licensed only in the member nation from which he provides telemedicine services, without regard to the location where the services are received.
License Requirement for International Telemedicine outside of EU or US	Many U.S. state medical boards do not have a clear opinion regarding physicians' remote medical services to patients outside of the United States.	"Country-of-Origin" Doctrine based on EU eCommerce Directive of 2000: License is required in nation where physician is located without regard to the location where the services are received.
Reimbursement for Telemedicine Consultation	Some form of telemedicine parity law has been adopted by at least 31 states. As each state has adopted different telemedicine parity laws, there is no uniform reimbursement standard across state lines. Federal Medicare Telehealth Parity Act (HR 2948, pending)	Directive 2011/24/EU: EU patients have a right to receive medical treatment in member nations, and be reimbursed under given circumstances. Directive 2011/24/EU Article 7: Member nations can require prior authorization for reimbursement of telemedicine services.
Digitization of Health Records, and Use of EMRs	EMR use is increasing after ACA	National EMRs adopted in many countries
Can the Patient access their records online?	Some EMRs allow patient access	Many national EMRs allow patient access (e.g. Denmark and Spain) and others are working towards providing access.
Legislation or Standards for Interoperability	The 21st Century Cure Act passed in 2016 requires interoperability of EHR and panelizes data blocking. Specifics of possible interoperability standards are being investigated by various organizations.	2013 Guideline for Cross-Border Directive 2011/24/EU: European Commission eHealth Network established a minimum/non-exhaustive patient summary dataset for electronic data exchange. 2014 Guideline for Directive 2011/24/EU: European Commission eHealth Network established an ePrescription dataset for electronic exchange. EC eHealth Network is working together to progressively achieve interoperability across EHRs of member nations (EC eHealth OECD study 11/2016)

TABLE: U.S. and Europe Telemedicine Laws and Regulations

for telemedicine so that physicians licensed in one nation could provide telemedicine services to patients who

reside in other EU nations without needing to obtain medical licenses

Continued on p. 47

from these nations.³ Furthermore, linguistic experts from several nations of the EU have been working together to develop ways of automatically translating and instantly delivering patient records to physicians, as appropriate.¹

The state medical boards of the U.S, however, have struggled with efforts designed to achieve similar legislative changes. In most states, physicians are required to be licensed in both the state where they practice and the state where the patient resides.⁴ For example, a Texas physician is required to obtain a Georgia medical license in advance of providing telemedicine care to a patient in Georgia to ensure that their services are legal and reimbursable by insurance.⁴ While some states now provide a telemedicine license or expedite multistate licensing, these measures are insufficient to support the widespread practice of interstate telemedicine.⁴ With current regulations, obtaining medical licenses in all 50 states for telemedicine practice is impractical and prohibitively expensive for health care providers and organizations.

U.S. medical licensure requirements for telemedicine practice are comparable to EU regulations

before 2000. Furthermore, U.S. telemedicine reimbursement regulations arbitrarily differ across state borders, and electronic medical record systems from various companies do not communicate properly with each other. At this time, physicians in the United States cannot retrieve patient records for unscheduled patient encounters in real-time unless the patient was previously treated using the same medical health records system, causing inconvenience to patients, treatment delays and duplicative medical testing.⁵

Similar to the European approach, we recommend that the state medical boards allow physicians licensed in one state to provide telemedicine services to patients in other states. Furthermore, we recommend collaboration among the state medical boards, industry leaders, and state legislatures to come up with uniform telemedicine reimbursement regulations and to design a uniform electronic medical record interoperability standard to allow the U.S. telemedicine industry to keep abreast of the global developments in telemedicine.

REFERENCES

1. Commission of the European Communities, Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Telemedicine for the Benefit of Patients, Healthcare Systems and Society. Brussels, 4.11.2008. COM(2008)639 final. (Accessed Oct. 24, 2017, at <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52008DC0689&qid=1508903557155&from=EN>)
2. eHealth Network, Guideline on an Organisational Framework for eHealth National Contact Point, adopted by consensus by the eHealth Network, Brussels, 23 November 2015. (Accessed Oct. 22, 2017, at https://ec.europa.eu/health/sites/health/files/ehealth/docs/ev_20151123_c001_en.pdf)
3. Raposo VL. GMS health technology assessment: Telemedicine: The legal framework (or the lack of it) in Europe. GMS Health Technology Assessment. 2016, Vol. 12, ISSN 1861-8863.
4. Thomas L, Capistand G. 50 State Telemedicine Gaps Analysis: Physician Practice Standards & Licensure, American Telemedicine Association, February 2017. (Accessed Oct. 24, 2017, at <http://utn.org/resources/downloads/50-state-telemedicine-gaps-analysis-physician-practice-standards-licensure.pdf>)
5. Prognosis, The Physician's Guide to Telemedicine in 2017. Bizmatrics. Inc. (Accessed Oct. 24, 2017, at <http://prognosis.com/wp-content/uploads/2017/01/Telemedicine-Whitepaper.pdf>)

Understanding Nurse, Family, and Interpreter Involvement in Family-Centered Rounds at Children's National Health System

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When contacted	Present at all (%)	Present entire time (%)	Present part time (%)	Average time of rounds missed (min)
Before Rounds (n=215)	76.28	30.70	45.58	00:02:21
At start/after rounds (n=82)	58.54	1.22	57.32	00:03:31
Not at all (n=135)	55.56	28.15	27.41	00:01:25

TABLE 1: Nurse Data

Family-Centered Rounds (FCR) is defined as a model that emphasizes bedside rounding as intentional inclusion of the patient and family in partnership with physicians, nurses, and staff.¹ Though families have generally reported positive experiences with FCR², limited English proficiency (LEP) families often face additional challenges due to inadequate provision of a licensed interpreter.³ Children's National Health System (Children's National) has been utilizing the FCR model with success for several years, however, the current protocol lacks a reliable and consistent notification system for all parties. Nurse, family, and interpreter involvement in FCR at Children's National could be enhanced by developing a specialized FCR mobile application to improve communication and coordination between the various stakeholders involved in a child's care.

The goal of the study was to collect and analyze data concerning the process of nurse, interpreter, and family inclusion in FCR at Children's

National. We used REDCap⁴ to design data collection instruments that were completed daily via objective observation while accompanying academic hospitalist teams on morning FCR. The data collected included measures of medical team communication with nurses, stakeholder presence at rounds, and provision of a licensed interpreter for LEP families.

One aim of our study was to examine current attendance rates for all parties involved in successful completion of FCR: bedside nurses, families, and interpreters. Medical teams contacted nurses only 59% of the time for FCR, which negatively affected nurse attendance rates (Table 1). Additionally, when the nurse was contacted it affected nurse presence and the amount of information missed on rounds. When nurses were contacted before rounds started, their presence increased by 31% compared to nurses who were contacted at the start/after rounds started (Table 1). The average time of rounds missed

also decreased by 1 minute and 10 seconds. Additionally, more nurses were present the entire time when contacted before rounds, as compared to being contacted at or after the start of rounds or not at all. This demonstrates the importance of giving nurses adequate time to get to rounds, a task which can be better facilitated by a mobile app notification system.

Nurses are an extremely important source of information when it comes to patient care: they have the most accurate knowledge of a patient's well-being, diet, and excretion, which are extremely important in creating a patient's daily care plan during rounds. The nurses also implement the plan created by the doctors, so including them in FCR is imperative for better patient care.

Another aim of our study examined family presence and involvement during FCR, especially comparing English proficient (EP) and LEP families. LEP families were present

Continued on p. 49

Continued from p. 48

more often than EP families for FCR, but were offered FCR less frequently (Table 2). Notably, a licensed interpreter was offered only 58% of the time for LEP families. This demonstrates that language is a barrier in facilitating FCR and protocol changes are needed to eliminate this disparity.

This study demonstrates a need to better facilitate FCR among doctors, nurses, families, and interpreters at Children's National. The preliminary data shows low nurse attendance, disparities in FCR being offered to LEP vs. EP families, and a lack of licensed interpreter use. We hope that technology, such as a mobile app notification system, can facilitate

better communication and coordination between all parties, ultimately improving patient care.

REFERENCES

1. Sisterhen LL, Blaszak RT, Woods MB, Smith CE. Defining family-centered rounds. *Teach Learn Med.* 2007;19(3):319-22.
2. Mittal V. Family-centered rounds: a decade of growth. *Hosp Pediatr.* 2014;4(1):6-8.
3. Walker-Vischer L, Hill C, Mendez SS. The experience of Latino parents of hospitalized children during family-centered rounds. *J Nurs Adm.* 2015;45(3):152-7.
4. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-81.

	Present at all (%)	FCR Offered (%)	FCR Accepted (%)	Licensed Interpreter Offered (%)
English Proficient (EP)	79.80	87.19	97.13	N/A
Limited English Proficiency (LEP)	88.06	79.66	95.74	58.73

TABLE 2: Family Data

Fusion

Fusion is the annual, student-run scientific journal of The George Washington University School of Medicine and Health Sciences William H. Beaumont Medical Research Honor Society.

Fusion was created to showcase medical student achievements in basic science and clinical research, clinical public health, medical education, and global health research. Submissions are requested from medical students annually in the fall.

