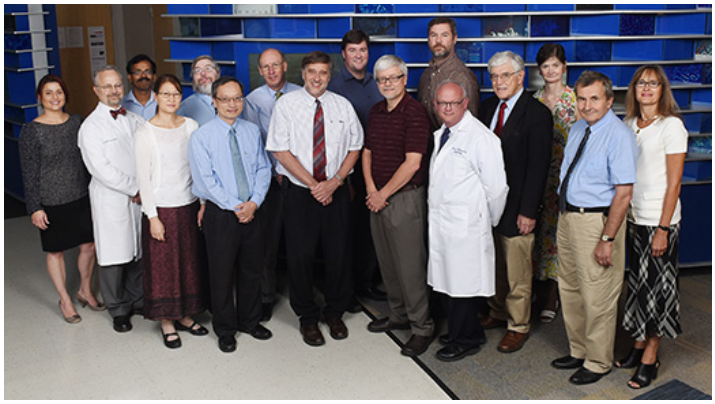
Cincinnati Children's

2015 Research Annual Report

# Pathology and Laboratory Medicine

RESEARCH AND TRAINING DETAILS



*Click to view members*

| | |
|---|---|
| Faculty | **23** |
| Research Fellows | **1** |
| Direct Annual Grant Support | **$920,126** |
| Direct Annual Industry Support | **$47,541** |
| Peer Reviewed Publications | **55** |

CLINICAL ACTIVITIES AND TRAINING

| | |
|---|---|
| Clinical Fellows | **2** |
| Inpatient Encounters | **688,474** |
| Outpatient Encounters | **700,537** |

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## Division Publications


1. Adams AK, Hallenbeck GE, Casper KA, Patil YJ, Wilson KM, Kimple RJ, Lambert PF, Witte DP, Xiao W, Gillison ML, Wikenheiser-Brokamp KA, Wise-Draper TM, Wells SI. **DEK promotes HPV-positive and -negative head and neck cancer cell proliferation**. *Oncogene*. 2015; 34:868-77.

2. Akeno N, Miller AL, Ma X, Wikenheiser-Brokamp KA. **p53 suppresses carcinoma progression by inhibiting mTOR pathway activation**. *Oncogene*. 2015; 34:589-99.

3. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, Mukkada VA, Succop PA, Abonia JP, Foote H, Eby MD, Grotjan TM, Greenler AJ, Dellon ES, Demain JG, Furuta GT, Gurian LE, Harley JB, Hopp RJ, Kagalwalla A, Kaul A, Nadeau KC, Noel RJ, Putnam PE, von Tiehl KF, Rothenberg ME. **Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis**. *J Allergy Clin Immunol*. 2014; 134:1084-1092 e1.

4. Bove KE, Olpin S. **The Metabolic Disease Autopsy**. In: MC Cohen, I Scheimberg, eds. *The Pediatric and Perinatal Autopsy Manual*. Cambridge, UK: Cambridge University Press; 2014:120-138.

5. Brahimaj B, Greiner HM, Leach JL, Horn PS, Stevenson CB, Miles L, Byars A, Holland K, Sutton M, Mangano FT. **The surgical management of pediatric brain tumors causing epilepsy: consideration of the epileptogenic zone**. *Childs Nerv Syst*. 2014; 30:1383-91.

6. Burrow TA, Sun Y, Prada CE, Bailey L, Zhang W, Brewer A, Wu SW, Setchell KD, Witte D, Cohen MB, Grabowski GA. **CNS, lung, and lymph node involvement in Gaucher disease type 3 after 11years of therapy: Clinical, histopathologic, and biochemical findings**. *Mol Genet Metab*. 2015; 114:233-41.

7. Butz BK, Wen T, Gleich GJ, Furuta GT, Spergel J, King E, Kramer RE, Collins MH, Stucke E, Mangeot C, Jackson WD, O'Gorman M, Abonia JP, Pentiuk S, Putnam PE, Rothenberg ME. **Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis**. *Gastroenterology*. 2014; 147:324-33 e5.

8. Caldwell JM, Collins MH, Stucke EM, Putnam PE, Franciosi JP, Kushner JP, Abonia JP, Rothenberg ME. **Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome**. *J Allergy Clin Immunol*. 2014; 134:1114-24.

9. Chlon TM, Hoskins EE, Mayhew CN, Wikenheiser-Brokamp KA, Davies SM, Mehta P, Myers KC, Wells JM, Wells SI. **High-risk human papillomavirus E6 protein promotes reprogramming of Fanconi anemia patient cells through repression of p53 but does not allow for sustained growth of induced pluripotent stem cells**. *J Virol*. 2014; 88:11315-26.

10. Cui Y, Tong H, Du X, Li B, Gale RP, Qin T, Liu J, Xu Z, Zhang Y, Huang G, Jin J, Fang L, Zhang H, Pan L, Hu N, Qu S, Xiao Z. **Impact of TET2, SRSF2, ASXL1 and SETBP1 mutations on survival of patients with chronic myelomonocytic leukemia**. *Exp Hematol Oncol*. 2015; 4:14.

11. Dong Z, Meller J, Succop P, Wang J, Wikenheiser-Brokamp K, Starnes S, Lu S. **Secretory phospholipase A2-IIa upregulates HER/HER2-elicited signaling in lung cancer cells**. *Int J Oncol*. 2014; 45:978-84.

12. Feldon M, Sikora K, Huggins JL, Billings SD, McMasters R, Brunner HI. **Polyarticular arthritis and skin nodulosis in a 14 year old female**. *Arthritis Care Res (Hoboken)*. 2014; .

13. Gupta A, Bischoff A, Pena A, Runck LA, Guasch G. **The great divide: septation and malformation of the cloaca, and its implications for surgeons**. *Pediatr Surg Int*. 2014; 30:1089-95.

14. Gupta N, Vassallo R, Wikenheiser-Brokamp KA, McCormack FX. **Diffuse Cystic Lung Disease. Part I**. *Am J Respir Crit Care Med*. 2015; 191:1354-66.

15. Gupta SK, Vitanza JM, Collins MH. **Efficacy and safety of oral budesonide suspension in pediatric patients with eosinophilic esophagitis**. *Clin Gastroenterol Hepatol*. 2015; 13:66-76 e3.

16. Harrington SM, Buchan BW, Doern C, Fader R, Ferraro MJ, Pillai DR, Rychert J, Doyle L, Lainesse A, Karchmer T, Mortensen JE. **Multicenter evaluation of the BD max enteric bacterial panel PCR assay for rapid detection of Salmonella spp., Shigella spp., Campylobacter spp. (C. jejuni and C. coli), and Shiga toxin 1 and 2 genes**. *J Clin*

*Microbiol*. 2015; 53:1639-47.

17. Heubi JE, Setchell KD, Jha P, Buckley D, Zhang W, Rosenthal P, Potter C, Horslen S, Suskind D. **Treatment of bile acid amidation defects with glycocholic acid**. *Hepatology*. 2015; 61:268-74.

18. Jeng MR, Fuh B, Blatt J, Gupta A, Merrow AC, Hammill A, Adams D. **Malignant transformation of infantile hemangioma to angiosarcoma: response to chemotherapy with bevacizumab**. *Pediatr Blood Cancer*. 2014; 61:2115-7.

19. Kesarwani M, Huber E, Kincaid Z, Azam M. **A method for screening and validation of resistant mutations against kinase inhibitors**. *J Vis Exp*. 2014; .

20. Kessler CA, Stanek JW, Stringer KF, Handwerger S. **ETS1 induces human trophoblast differentiation**. *Endocrinology*. 2015; 156:1851-9.

21. Kohli R, Myronovych A, Tan BK, Salazar-Gonzalez RM, Miles L, Zhang W, Oehrle M, Sandoval DA, Ryan KK, Seeley RJ, Setchell KD. **Bile Acid Signaling: Mechanism for Bariatric Surgery, Cure for NASH?**. *Dig Dis*. 2015; 33:440-6.

22. Kuhn MW, Hadler MJ, Daigle SR, Koche RP, Krivtsov AV, Olhava EJ, Caligiuri MA, Huang G, Bradner JE, Pollock RM, Armstrong SA. **MLL partial tandem duplication leukemia cells are sensitive to small molecule DOT1L inhibition**. *Haematologica*. 2015; 100:e190-3.

23. Li B, Xu J, Li C, Gale RP, Xu Z, Qin T, Zhang Y, Huang G, Fang L, Zhang H, Pan L, Hu N, Qu S, Xiao Z. **Cytogenetic studies and their prognostic contribution in 565 Chinese patients with primary myelofibrosis**. *Am J Hematol*. 2014; 89:1043-6.

24. Lombardi AJ, Hoskins EE, Foglesong GD, Wikenheiser-Brokamp KA, Wiesmuller L, Hanenberg H, Andreassen PR, Jacobs AJ, Olson SB, Keeble WW, Hays LE, Wells SI. **Acquisition of Relative Interstrand Crosslinker Resistance and PARP Inhibitor Sensitivity in Fanconi Anemia Head and Neck Cancers**. *Clin Cancer Res*. 2015; 21:1962-72.

25. Martin LJ, Franciosi JP, Collins MH, Abonia JP, Lee JJ, Hommel KA, Varni JW, Grotjan JT, Eby M, He H, Marsolo K, Putnam PE, Garza JM, Kaul A, Wen T, Rothenberg ME. **Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease**. *J Allergy Clin Immunol*. 2015; 135:1519-1528 e8.

26. McCauley HA, Liu CY, Attia AC, Wikenheiser-Brokamp KA, Zhang Y, Whitsett JA, Guasch G. **TGFbeta signaling inhibits goblet cell differentiation via SPDEF in conjunctival epithelium**. *Development*. 2014; 141:4628-39.

27. Merrow AC, Gupta A, Adams DM. **Additional imaging features of intramuscular capillary-type hemangioma: the importance of ultrasound**. *Pediatr Radiol*. 2014; 44:1472-4.

28. Misch C, Tang P. **Therapeutic drug monitoring of mycophenolic acid and its glucuronide by HPLC/UV**. *Clin Lab Int*. 2015; :28-31.

29. Moon C, Zhang W, Ren A, Arora K, Sinha C, Yarlagadda S, Woodrooffe K, Schuetz JD, Valasani KR, de Jonge HR, Shanmukhappa SK, Shata MT, Buddington RK, Parthasarathi K, Naren AP. **Compartmentalized accumulation of cAMP near complexes of multidrug resistance protein 4 (MRP4) and cystic fibrosis transmembrane conductance regulator (CFTR) contributes to drug-induced diarrhea**. *J Biol Chem*. 2015; 290:11246-57.

30. Mortensen JE, Ventrola C, Hanna S, Walter A. **Comparison of time-motion analysis of conventional stool culture and the BD MAX Enteric Bacterial Panel (EBP)**. *BMC Clin Pathol*. 2015; 15:9.

31. Osborn AJ, Dickie P, Neilson DE, Glaser K, Lynch KA, Gupta A, Dickie BH. **Activating PIK3CA alleles and**

**lymphangiogenic phenotype of lymphatic endothelial cells isolated from lymphatic malformations**. *Hum Mol Genet*. 2015; 24:926-38.

32. Peelukhana SV, Goenka S, Kim B, Kim J, Bhattacharya A, Stringer KF, Banerjee RK. **Effect of higher frequency components and duration of vibration on bone tissue alterations in the rat-tail model**. *Ind Health*. 2015; 53:245-59.

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34. Rams TE, Feik D, Mortensen JE, Degener JE, van Winkelhoff AJ. **Antibiotic susceptibility of periodontal Streptococcus constellatus and Streptococcus intermedius clinical isolates**. *J Periodontol*. 2014; 85:1792-8.

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39. Shannon JM, Wikenheiser-Brokamp KA, Greenberg JM. **Lung Growth and Development**. In: C Broaddus, RJ Mason, eds. *Murray & Nadel's Textbook of Respiratory Medicine*. Philadelphia, PA: Saunders (Elsevier); 2015:22-31.

40. Sheridan R, Belludi C, Khoury J, Stanek J, Handwerger S. **FOXO1 expression in villous trophoblast of preeclampsia and fetal growth restriction placentas**. *Histol Histopathol*. 2015; 30:213-22.

41. Sherrill JD, Kiran KC, Blanchard C, Stucke EM, Kemme KA, Collins MH, Abonia JP, Putnam PE, Mukkada VA, Kaul A, Kocoshis SA, Kushner JP, Plassard AJ, Karns RA, Dexheimer PJ, Aronow BJ, Rothenberg ME. **Analysis and expansion of the eosinophilic esophagitis transcriptome by RNA sequencing**. *Genes Immun*. 2014; 15:361-9.

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**delivery**. *J Perinat Med*. 2014; 42:457-71.

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52. Weaver KN, Wang D, Cnota J, Gardner N, Stabley D, Sol-Church K, Gripp KW, Witte DP, Bove KE, Hopkin RJ. **Early-Lethal Costello Syndrome Due to Rare HRAS Tandem Base Substitution (c.35_36GC>AA; p.G12E)-Associated Pulmonary Vascular Disease**. *Pediatr Dev Pathol*. 2014; 17:421-30.

53. Weiss B, Ratner N, Sheil AT. **Malignant Peripheral Nerve Sheath Tumors**. In: M Karajannis, D Zagzag, eds. *Molecular Pathology of Nervous System Tumors : Biological Stratification and Targeted Therapies*. New York: Springer; 2014:213-224.

54. Wiederhold NP, Sutton DA, Li DW, Liang Y, Thompson EH, Wickes BL, Herrera ML, Rhoads SL, Mortensen JE. **Stachybotrys eucylindrospora isolated from foreign material following a traumatic eye injury**. *Mycoses*. 2014; 57:437-41.

55. Xu YH, Xu K, Sun Y, Liou B, Quinn B, Li RH, Xue L, Zhang W, Setchell KD, Witte D, Grabowski GA. **Multiple pathogenic proteins implicated in neuronopathic Gaucher disease mice**. *Hum Mol Genet*. 2014; 23:3943-57.

# Faculty, Staff, and Trainees

### Faculty Members

**David Witte, MD**, Professor

**Leadership** Division Director

**Research Interests** Renal pathology, molecular pathology

**Mohammad Azam, PhD**, Assistant Professor

**Research Interests** Cancer Biology and Neural Tumors Program

**Michael Baker, MD**, Assistant Professor

**Research Interests** Pulmonary pathology, Cardiac pathology

**Kevin E Bove, MD**, Professor

**Research Interests** Pediatric liver disease, biliary atresia

**Margaret H Collins, MD**, Professor

**Research Interests** Pediatric gastrointestinal pathology, especially pediatric eosinophilic gastrointestinal disorders, pediatric inflammatory bowel disease, pediatric bowel motility disorders

**Anita Gupta, MD**, Associate Professor

**Research Interests** Liver tumor pathology, vascular anomalies

**Gang Huang, PhD**, Assistant Professor

**Research Interests** Cancer pathology

**Robert Lorsbach, MD, PhD**, Professor

**Leadership** Director, Hematopathology Service

**Research Interests** Hematopathology

**Richard L McMasters, MD**, Assistant Professor

**Research Interests** Hematopathology

**Lili Miles, MD**, Associate Professor

**Leadership** Director, Training Program

**Research Interests** Brain tumor, epilepsy research, neuromuscular diseases and NASH liver

**Joel E Mortensen, PhD**, Associate Professor

**Leadership** Director, Diagnostic Infectious Disease Lab

**Research Interests** Microbiology

**Lindsey Romick-Rosendale, PhD**, Assistant Professor

**Research Interests** Metabolomics

**Kenneth D Setchell, PhD**, Professor

**Leadership** Director, Mass Spec Lab

**Research Interests** Biochemistry,Bile acids,Sterol and cholesterol metabolism,Steroids, Liver disease, Liver transplantation, Gastroenterology, Nutrition/Diet, Phytochemicals, Isoflavones/Lignans, Breast cancer, Colon cancer, Mass spectrometry – biomedical mass spectrometry, Chromatography, Analytical Biochemistry, Assay development, Therapeutic drug monitoring, Pharmacokinetics and metabolism, Genetics

**S. Kumar Shanmukhappa, PhD**, Assistant Professor

**Research Interests** Experimental animal models

**Amy Sheil, MD**, Assistant Professor

**Rachel Sheridan, MD**, Assistant Professor

**Research Interests** Liver pathology, biliary atresia

**Jerzy W Stanek, MD, PhD**, Professor

**Research Interests** Pathology and pathomechanisms of in-utero hypoxia, particularly in the placenta; Pathology of perinatal mortality and morbidity

**Paul E Steele, MD**, Associate Professor

**Leadership** Medical Director, Clinical Lab

**Research Interests** Clinical lab medicine

**Keith F Stringer, MD**, Assistant Professor

**Research Interests** Microscopic techniques for assessing mRNA expression, protein production and cellular identity in eukaryotic tissues

**Peter Tang, PhD**, Associate Professor

**Research Interests** Special chemistry

**Dehua Wang, MD**, Assistant Professor

**Research Interests** Hematopathology

**Mikako Warren, MD**, Assistant Professor

**Research Interests** Renal pathology

**Kathryn Wikenheiser-Brokamp, MD, PhD**, Associate Professor

**Research Interests** Genetic and developmental basis of lung disease, lung cancer and pediatric cystic lung disease

### Trainees

- **Daniel Leino, MD**, PL-6, University of Michigan
- **Jessica Hata, MD**, PL-5, Vanderbilt Universtiry

# Grants, Contracts, and Industry Agreements

| Grant and Contract Awards | | Annual Direct |
|---|---|---|

### Azam, M

**Therapeutic Targeting of De Novo and Acquired Resistance in Childhood Leukemia**

Cancer Free Kids

| | 7/1/2014-6/30/2015 | $50,000 |
|---|---|---|

**Improved Therapeutic Approaches for Hematological Disorder Treated with Tyrosine**

National Institutes of Health

| R01 CA155091 | 5/1/2012-3/31/2017 | $207,500 |
|---|---|---|

### Huang, G

**Role of the Hypoxia-Inducible Factor-1alpha in Myelodysplastic Syndromes**

National Institutes of Health

| R01 DK105014 | 3/1/2015-2/29/2020 | $225,000 |
|---|---|---|

**A Novel Epigenetic Circuit in Acute Leukemia**

National Cancer Institute

| | | |
|---|---|---|
| R21 CA187276 | 7/9/2014-6/30/2016 | $108,750 |

**A Novel Epigenetic Circuit In Acute Leukemia**

When Everyone Survives Foundation

| | | |
|---|---|---|
| | 7/1/2014-6/30/2015 | $37,037 |

## Wagh,P

**p130 and Pim-1 as Prognostic Biomarkers and Therapeutic Targets in Lung Cancer**

National Institutes of Health

| | | |
|---|---|---|
| F32 CA89685 | 7/1/2014-8/31/2016 | $54,853 |

## Wikenheiser-Brokamp, K

**Mechanisms Underlying DICER1 Suppression of Pleuropulmonary Blastoma Initiation**

St. Baldrick's Foundation

| | | |
|---|---|---|
| | 7/1/2011-6/30/2016 | $132,970 |

**Hypoxia Signaling and Spontaneous Pulmonary Fibrosis in a Novel Mouse Model**

National Institutes of Health (University of South Florida)

| | | |
|---|---|---|
| R21 AG047473 | 01/15/2015-12/31/2016 | $23,050 |

## Witte, D

**Digestive Health Center: Bench to Bedside Research in Pediatric Digestive Disease - Integrative Morphology Core**

National Institutes of Health

| | | |
|---|---|---|
| P30 DK 078392 | 06/01/2012-05/31/2017 | $80,966 |

| | |
|---|---|
| **Current Year Direct** | **$920,126** |

## Industry Contracts

## Collins, M

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|---|---|
| Meritage Pharma, Inc | $41,295 |

## Mortensen, J

| | |
|---|---|
| Research Triangle Institute | $6,246 |

| | |
|---|---|
| **Current Year Direct Receipts** | **$47,541** |

| | |
|---|---|
| **Total** | **$967,667** |

# Glycocholic Acid Proves Effective Against Newly Identified Amidation Defect

Kenneth Setchell, PhD

James Heubi, MD

RESEARCH AND TRAINING DETAILS

| | |
|---|---|
| Faculty | 23 |
| Research Fellows | 1 |
| Direct Annual Grant Support | $920,126 |
| Direct Annual Industry Support | $47,541 |
| Peer Reviewed Publications | 55 |

Heubi JE, Setchell KD, Jha P, Buckley D, Zhang W, Rosenthal P, Potter C, Horslen S, Suskind D. Treatment of bile acid amidation defects with glycocholic acid. *Hepatology.* 2015;61(1):268-274.

PUBLISHED ONLINE DEC. 23, 2014
*Hepatology*

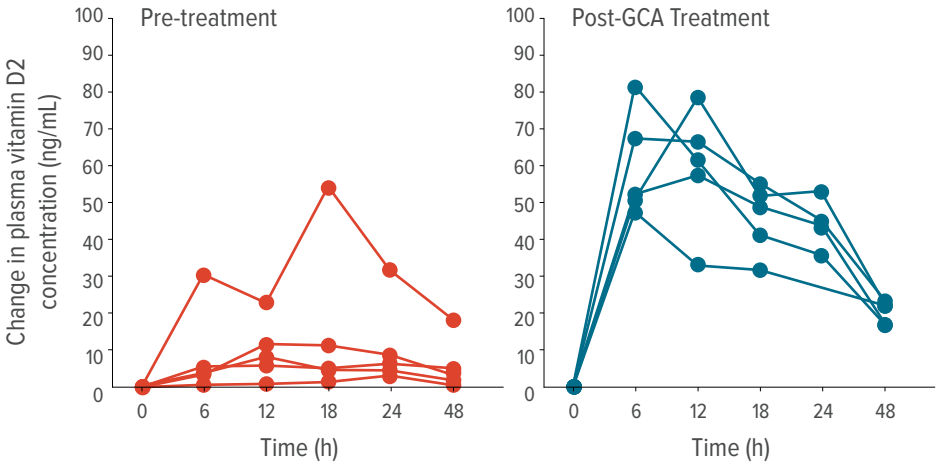
Over the past 30 years, James Heubi, MD, and Kenneth Setchell, PhD, have revolutionized the treatment of liver disease in children, and their novel findings led to the March 2015 FDA approval of the drug Cholbam. This bile acid treatment — when given to children — tricks the liver into thinking it is producing enough of its own healthy bile acid so that it shuts down production of defective bile acids that lead to liver disease.

Now, Heubi and Setchell have identified another liver enzyme irregularity called an amidation defect, in which the liver produces too much unconjugated cholic acid because the amino acids glycine or taurine cannot conjugate it effectively. Normally, cholic acid dissolves fats and helps the body excrete cholesterol.

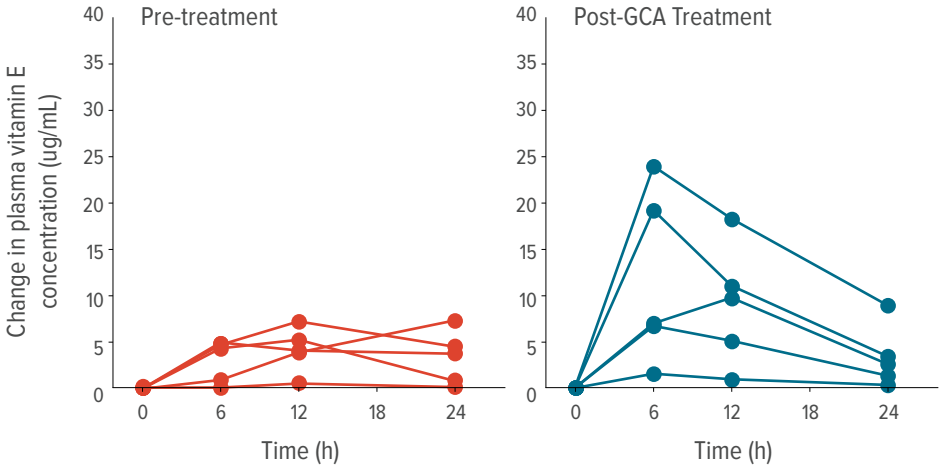
Heubi and Setchell identified five children with the amidation defect, all of whom showed mutations in the BAAT gene and exhibited failure to grow, vitamin absorption deficiencies or choleostasis. After treatment of up to 92 months with glycocholic acid (GCA), the patients were able to absorb the fat-soluble vitamins D-2 and tocopherol, showed improvement in growth, and experienced no side effects.

This is the sixth of 17 known liver enzyme defects that Heubi and Setchell have identified, and they are working on testing and funding for development of a GCA drug. Their work appeared online Dec. 23, 2014, in *Hepatology*.

"All of these defects manifest as fatal forms of liver disease if they're not diagnosed, and there is no other form of liver disease you can reverse like this," Setchell says. "This is lifelong therapy for all these kids. We believe that GCA should be the standard of care and supplemental fat-soluble vitamins should be the standard of care for affected patients."




Clinicians and scientists at Cincinnati Children's have identified and treated five patients with defective bile acid amidation due to a genetically confirmed deficiency in bile acid CoA:amino acid N-acyl transferase (BAAT) with the conjugated bile acid, glycocholic acid (GCA). These charts show changes from baseline in plasma vitamin D2 and tocopherol concentrations in response to a single oral bolus dose of vitamin D2 and tocopherol in patients with BAAT deficiency before and after treatment with glycocholic acid.




"This is lifelong therapy for all these kids. We believe that GCA should be the standard of care and supplemental fat-soluble vitamins should be the standard of care for affected patients."