STUDY 1 : Hepatology :Whom to do Kasai – Genetic signature?

Luo, Z., Shivakumar, P., Mourya, R., Gutta, S., & Bezerra, J. A. (2019). Gene Expression Signatures Associated With Survival Times of Pediatric Patients With Biliary Atresia Identify Potential Therapeutic Agents. Gastroenterology. doi:10.1053/j.gastro.2019.06.017

Factors that affect outcomes of patients with biliary atresia were studied in this paper. Liver biopsies and clinical data obtained from infants with cholestasis and without liver disease. Messenger RNA (mRNA) was isolated randomly assigned to discovery (n=121) and validation sets (n=50), and analyzed by RNA sequencing.14-gene mRNA expression pattern predicted shorter and longer survival times in both the discovery (n=121) and validation sets (n=50) of children with Biliary atresia. Gene expression signature combined with level of bilirubin at 3 months after hepato-portoenterostomy, identified children who survived for 24 months. Many mRNAs expressed at high levels in liver tissues with good survival had enriched scores for glutathione metabolism suggesting the importance of N acetyl Cysteine. While mRNAs encoding proteins that regulate fibrosis genes were increased in liver tissues from infants who did not survive for 2 years. For evaluation of surgical success, importance of underlying genetic factors is underscored. Thus 14-gene signature has the potential to change our approach to children with biliary atresia.

STUDY 2: Luminal Gastroenterology: What's the level of Calprotectin?

Kennedy, Nicholas A. et al. Association Between Level of Fecal Calprotectin and Progression of Crohn's Disease .Clinical Gastroenterology and Hepatology, Volume 17, Issue 11, 2269 - 2276.e4 https://doi.org/10.1016/j.cgh.2019.02.017

918 patients with Crohn's disease (CD) were examined retrospectively. Clinical data and fecal calprotectin measurements were analyzed .Median follow-up was of 50.6 months. A calprotectin level cut-off of 115 mcg/g was identified as optimal for separation of those with and without disease progression. Earlier studies have identified a cut-off value of 250 mcg/g as being useful to distinguish active from inactive disease. In this study a lower threshold of 115 mcg/g was identified suggesting that lower levels of inflammatory activity still may be associated with an adverse outcome.

STUDY 3: Hepatology: Interesting NASPGHAN Scientific abstract worth considering?

Machine learning models to predict waitlist mortality among pediatric liver transplant candidates: an update to PELD. Sonja Swenson , John Roberts , Emily Perito Pediatrics, University of California, San Francisco, Palo Alto, CA; Surgery, University of California, San Francisco, San Francisco, CA

No studies till now have examined whether Machine Learning techniques that could improve prediction modeling for pediatric liver transplant candidates. UNOS Standard Transplant Analysis and Research (STAR) data was used in the study. Machine Learning identified patterns and interactions in data that can improve prediction accuracy. 16 objective variables were evaluated for inclusion. Cohort included all U.S. liver transplant candidates. A Refit PELD was built with a multivariate Cox Proportional Hazards (PH) model using current PELD components. PELD+ was derived by backward stepwise regression as an expanded Cox PH model. RSF is a ML model that creates many independent decision trees; each form a unique data subset to determine the final model. Random Forest RSC (Rv.3.5.3) .It is used to produce 1000 trees grown under log-rank competing risks splitting. RSF's C-index was significantly higher than that of Refit PELD or PELD+. RSF's most important

predictors were bilirubin, INR, height z-score, age, albumin, creatinine, ascites and weight z-score. Thus ML techniques could improve mortality predictions for children awaiting liver transplant.

STUDY 4: Luminal Gastroenterology Monogenic vs Non-monogenic IBD: APPROACH?

Lega, S., Pin, A., Arrigo, S., Cifaldi, C., Girardelli, M., Bianco, A. M., ... Bramuzzo, M. (2019). Diagnostic Approach to Monogenic Inflammatory Bowel Disease in Clinical Practice: A Ten-Year Multicentric Experience. Inflammatory Bowel Diseases. doi:10.1093/ibd/izz178

Patients with VEO-IBD and early onset IBD with severe/atypical phenotypes (EO-IBD s/a)(n= 93) managed between 2008– 2017 who underwent a genetic workup were studied. In 13% a genetic diagnosis was confirmed. Candidate sequencing (CS) was performed in 50%, and next generation sequencing (NGS) was performed in 90%. Candidate sequencing had a good diagnostic performance when guided by clinical features specific for known monogenic diseases. NGS helped finding new causative genetic variants. 59% of patients in group <2 years of age.59% were males .8% had family history of IBD.Extra-intestinal manifestations were present in 43%.

Monogenic IBD group had <1 month onset .They were predominantly Boys .The coexistence of extraintestinal manifestation was noted in this group .Both Colonic and small bowel and/or perianal involvement was present. Sanger sequencing helped in diagnosis .Bone marrow transplant was useful in specific cases. Nonmonogenic IBD had later onset without gender bias. Extraintestinal manifestations were less likely.NGS: next generation sequencing helped in diagnosing these cases.

Add on: Common Genetic variants that cause VEOIBD are XIAP, IL10RA,G6PC3,MEFV, LRBA, FOXP3,and TTC7A. Genetic variants ZAP70, RAG2, IL2RG, LIG4, ADA, DCLRE1C, CD3G, are generally associated with immunodeficiency. New sequencing technologies are diagnosing more genetic variants which are associated with VEOIBD. Streamlining investigations would be helpful in resource poor settings. Easy availability of NGS may help in diagnosis in most cases with possibility of missing a few. Judicious approach based on clinical tell-tale signs with endoscopic findings may integrate both the approaches in future.

STUDY 5: Luminal Gastroenterology: Epigenetics in Celiac Disease: Mucosal biopsy?

Romero-Garmendia I, Garcia-Etxebarria K, Hernandez-Vargas H, et al. Transcription Factor Binding Site Enrichment Analysis in Co-Expression Modules in Celiac Disease. Genes (Basel). 2018;9(5):245. Published 2018 May 10. doi:10.3390/genes9050245

Transcription factor binding site enrichment analysis[5] in co-expression module in celiac disease was studied by Irati Romero-Garmendia et al .It is the first whole genome co-expression analytical study that tests the effect of gliadin in duodenum biopsies of pediatric patients. (n = 18) .Duodenal biopsies samples were immediately stored in liquid nitrogen. RNA was extracted later. In-vitro culture (with or without gliadin) of biopsy portion on two set of patients' viz. Celiac diagnosed on gluten free diet and celiac disease patient at diagnosis were studied. They noted transcription factor like IRF1, ELKI, NFKB1 and CREB1 were significantly up regulated in celiac disease. These were the key molecules which control gene expression. ELK1 transcription factor was over expressed at mRNA level in active celiac disease. ELK1 had an important role in deciding intestinal permeability.

Celiac disease is multi-factorial in etiology. Transcription factor analysis helps us to understand important role of epigenetics in pathophysiology.

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