Conferences 2016

Sungpil Han

2016-07-13

Contents

Chapter 1

Introduction

Chapter 2

2016 KSCPT

2.1 Opening Remark

- Yil-Seob Lee (president of KSCPT)

2.2 First Session

- Chair : Deborah Chee(KoNECT)

2.2.1 13:20~14:00 Precision Medicine: A Clinical Pharmacological Perspective

- Speaker: Munir Pirmohamed (University of Liverpool, UK)
- Fava beans - Favism G6PD deficiency - withrawal of antimalarials
- 2015 Obama Precision Medicine $215m / 2016 China $8b
- Phenotypic definition(current standard) - Molecular definition (disease stratification) - Drug variability
- Mandatory genomic testing - EMA SmPC
- Pharmacogenomics Journal (2015) 1-10
- Crizotinib vs CTx in advanced ALK+ lung cancer (NEJM 2013)
- Novel trial design (Nature 2015)

1. Umbrella trial (single tumor - multiple arm - multiple drugs)
2. Basket study

- Support of humen genetic evidence for approved drug indication (Nature Genetics)
- Sclerosteosis - skeletal overgrowth and syndactyly, AR , mutations in SOST gene - target sclerostin
- anti-sclerostin Ab (ROMOSOZUMAB, BLOSOZUMAB) - bone density increase - mouse
- New cardiovascular targets
- PCSK9 - GOF->LDL-C increase & CVD
- ANGPTL4
- HLA-genotype and carbamazepine-induced cutaneous ADR: systemic review (CPT,2012)
- ITCH (Drug hypersensitivity)
- Phase I, II - very strong association (Manhattan plot) - GWAS - ALK(germline polymorphism-> T cell expansion)
- SJS GWAS (Genin 2011) http://www.ncbi.nlm.nih.gov/pubmed/21801394
- Skin, Liver
- CBZ-induced hypersensitivity vs CBZ-tolerant patients

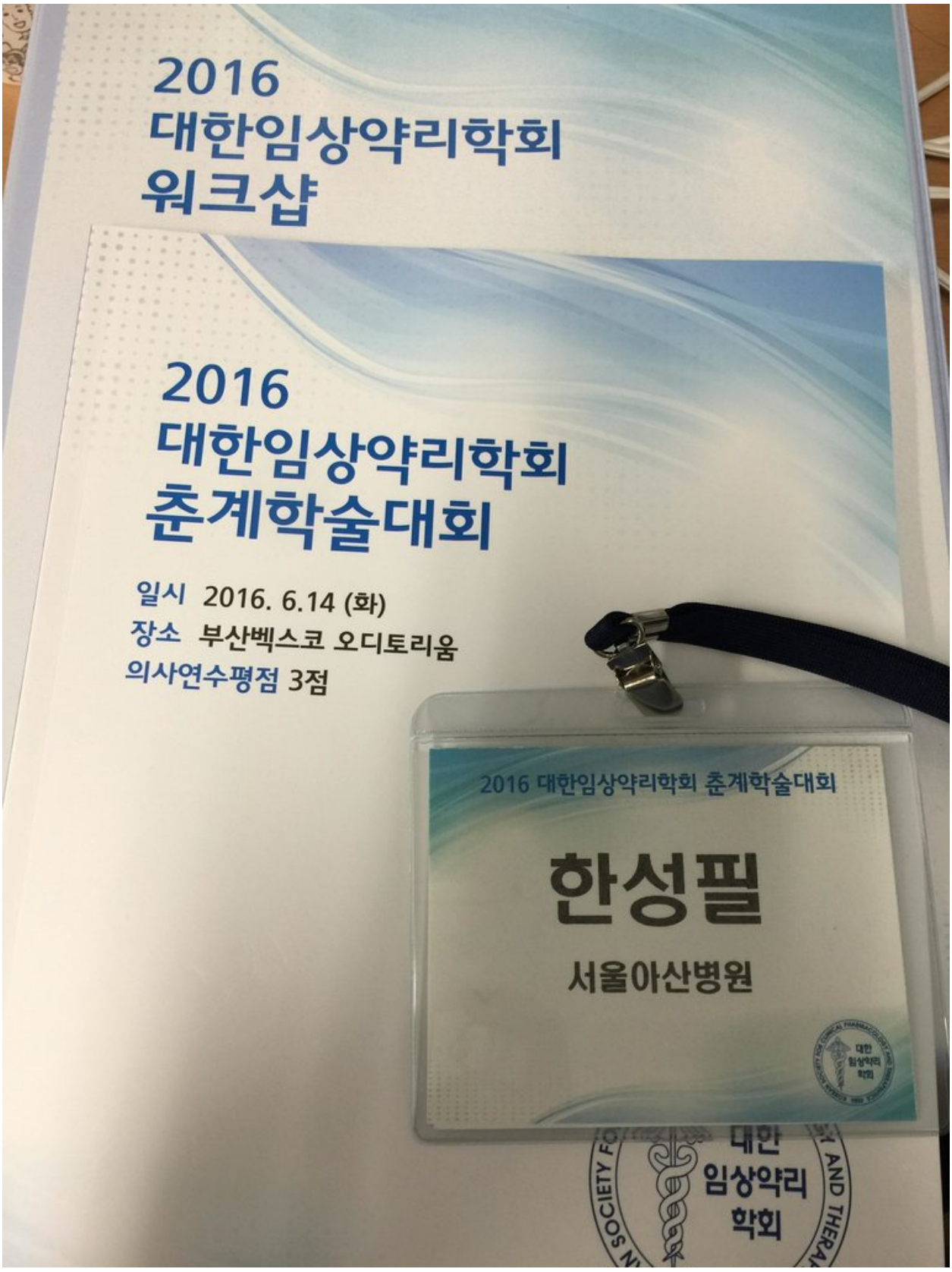

Figure 2.1: Materials

- HLA-A*31:01(thirtyone o one)
- HLA and ADR
- The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. (2016) http://www.ncbi.nlm.nih.gov/pubmed/26478982
- Somatic genomes -> microbiome is also important
- Digoxin and antibiotics (1981, NEJM) -> (2013 Science) Cardiac drug inactivation by human gut bacteria
- Microbiome and Cancer Immunotherapy - Snyder, Science Nov 2015
- Two books introduced.

1. Prescription for nhs
2. clinical pharma dynamic medical specialty

2.2.2 14:00~14:30 The role of pharmacogenomics in drug development, regulatory review and clinical practice

- Speaker: Shiew-Mei Huang (North Potomac, MD, USA)
- CPIC (Clinical pharmacogenetics guidelines)
- IFNL3(IL28B) HCV treatment Favorable response = 77% Asian (Genotype CC)
- Paving the way for Personalized Medicine (Oct 2013)
- Avacavir HLA-B*5701 (RCT) Utility of pharmacogenetic tests
- Munir mentioned - CBZ & HLA-B*1502
- ASCO meeting - CTx vs Targeted therapy - Umbrella study
- Drug labeling “FDA-approved test”
- XALKORI - Crizotinib and ALK
- CPT Feb 2016 - Precision Medicine , “Companion Diagnostics” Something unique to conduct , “Complementary diagnostics”
- Eliglustat and CYP2D6 , Drug labeling
- Center for Device
- Integral to the future of personalized or precision medicine
- NGS
- PrecisionFDA initiative
- 23andMe - Drug response , Confidence
- Cleared or approved FDA
- CLIA-certified laboratory

2.2.2.1 My Question

- One NGS - individual test to is there a review of all-in-one Test in progress?

2.2.3 14:30~15:00 The Liver-Gut Microbiota Axis Modulates Inter-Individual Variability in Xenobiotic Disposition and Toxicology

- Speaker: Eric Chun Yong Chan (National University of Singapore)
- Liver - major organ for disposition and detoxification
- 60% (explanble) vs 40% (how about this?) - superorganism
- 400 different species (~1.5kg)
- Haiser (2012, Science) Gut microbe - drug, host interaction
- TOC: 1 DMD paper , 2 in-house project
- DMD - reduction, hydrolysis
- absorption - simvastatin - poor responder, average, good 10% 80% 10%

  - OATP1B1 in liver and intestine
  - Possibility of competition between simvastatin and bile acids for hepatic uptake by transporter
  - antibiotics - nitro-reduction by gut microbiota inhibition
  - Therapeutic fficacy - DDI
- PCA analysis PNAS 2009 - significant differences in concentration
- PNAS 2009 inverse corr - p-cresol <-> AAP
- 2nd part - Tacrine - first drug approved for AD. Toxicological manifestation - increased AST/ALT
- Interindividual variability. why?
- Tacrine metabolism - hydroxylation / glucuronide
- mitochondrial toxicity and hypoxia-reoxygenation
- part I~V
- Tacrine-induced transaminitis
- EXT - CMax,AUC high why? - phase II metabolite?
- host gene - mRNA
- GC/TO
- PCA analysis principal component analysis
- NORMAL Lactobacillus
- EXT Bacteriode Blautia
- Metagenome level
- Liver - Tacrine-> TacrineNGlucuronide

2.3 Second Session

- Chair : Yong-Bok Lee(Chonnam National University)

2.3.1 15:20~15:50 The role of stem cells in discovery and validation of pharmacogenomic markers

- Speaker : Eileen Dolan (The University of Chicago, USA)
- Ototoxicity, CTx Toxicity - hearing loss, peripheral neuropathy
- dose-limiting toxicity - platinum, taxanes, vinca, epothilones, bortezomib
- numbness, tingling, burning/stabbing pain
- partially , can be permanent
- Duloxetine - SNRI - CIPN
- pharmacogenomic studies - optimal model - testicular cancer -
- platinating agents
- CIPN - >300mg/m2, dorsal root g. cell apoptosis, affects large neurons, axonal projections
- CTCAE of CIPN, patient-reported measures preferred (CIPN EORTC-CPIN20)
- PCA analysis
- age, smoking
- GWAS - CIPN6 -> CAMTA1, RGS, WDR1, MAPK9, COA1, ILR2A
- Polygenic architecture
- PIPN : ECOG: rs3125923
- Stem cells - problems - identifying, priortizing
- cell-based PD analysis
- iPSC technology in PGx, CRISPR
- Neuronal measurements - total outgrowth processes, process length, branches, cell body area
- C, P, 5FU, Bortezomib, Vinc, Thalidomide
- inhibition of neurite outgrowth
- VIN - GWAS 2000 patients
- CEP72 - microtubules assembly, TT allele - susceptible -> lower CEP72 mRNA expression

- knockdown of CEP72 in iPCSC -> enhancing sensitivity to vincristine

2.3.1.1 Questions - neurite outgrowth

- Neurons- mature enough?

2.3.2 15:50~16:20 Pharmacogenomics and Epigenomics

- Speaker: Matthias Schwab (IKP Stuttgart, Germany)
- Prognostic predictors
- Genetic make-up
- 135 FDA-approved drugs with labeled pharmacogenomic information (2015-05-20)
- top 30 drugs with pharmacogenetic risk (w/ or w/o high-risk diplotype for gene)
- Genomics, proteomics metabolomics, microbiomics
- Genome Medicine 2016 (Auffray, Schwab)
- NEJM
- Cocktail approach - a single dose PK study - old fashion clinical pharmacology approach? -
- Metoprolol and Torsemide PK - heretability
- Koryza Genet Med 2016 - comprehensive analysis - ESP project (n=6500) and 1000 genomes project
- PNAS 2005 Fraga - Epigenomics and DNA methylation
- miRNA, methylation, histone modification(acetylation)
- CPT 2016, Fisel, Schaeffeler, Schwab - DNA methylation and its impact on disease pathophysioloy and drug therapy
- Heatmap - ADME genes - SLC transporters

2.3.2.1 My Quesion

- Can we develop therapeutics which target locus of epigenetic (Decitabine)- Renal cancer cell - treatment of decitabine - demethylating agents (Specificity?)
- Epigenomics

2.3.3 16:20~16:50 Emerging roles of human CYP1B1 in cancer growth and metastasis

- Speaker: Young-Jin Chun (Chung-Ang University, KOREA)
- P450 (CYP1B1)
- Estrogen metabolism : E2->4-OHE2(endogenous mutagen)
- ZYC300 cancer vaccine - CYP1B1 DNA Vaccine
- Immunity to CYP1B1 -> Clinical benefit
- 과발현시 - PCNA increased
- TMS - specific human CYP1B1 - DMBA->PPCNA increased, DMBA+TMS->PBNA back to normal
- CYP1B1 -> EMT (ECADHERIN, ZEB1, Vimentin, twist1) FUNCTIONAL STUDY , Can we transmembrane migration - cancer progression
- SP1 Transctiption factors - Mithramycin A(binding inhibittor) DMBA에의해 증가한 에스피1등이 mitA를 억제.
- 이러한 결과들을 통해서 SP1이 암 증식 chip assay
- 4OHE는 EMT 촉진된다.
- 억제 - Mithramycin A
- 촉진 - DMBA, CYP1B1, SP1, 4OHE
- Matrigel, migration -> migration, invasion

2.3.3.1

1B1에 의해 대사되는 irinotecan - 알수가 없다. Tumor 조직을 갖고 enzyme activity 측정전에. active metabolism 2D6는 steroid

2.3.4 16:50~17:20 omics for precision Medicine : Clinical Implementation in oncology

- Speaker: Kyu-pyo Kim (University of Ulsan College of Medicine, KOREA)
- effects are not immediate / severe adverse effects / narrow therapeutic window
- UGT1A1 genotypes - different enzyme activities , Irinotecan
- Irinotecan -> practical decision making - not reached.
- genotype information - strong enough?
- neutropenia, diarrhea
- mutations are abundant - mutational loading (high- melanoma, lung sq cel carcinoma)
- Point mutations, copy # variation -> omics + NGS -> clinical interpretation -> clinical decision making
- Ca Cancer J Clin 2016 - 1 month TIME IS IMPORTANT FOR PATIENTS.
- Issues : Forces or hurdles - COSTS - volume of patients/turnaround time/Central testing/Quality control
- NCI-Match - somatic mutation - Oncomine Comprehensive Assay Gene List - How to report???
- KRAS A146 mutation in CRC -> CTX guideline - clinical trial
- CPCM - KCSG 11th methodology -
- Transition : from research to practice - CLIA (23andMe)
- NGS 임상검사실 인증제도 추진중임.
- Summary - abundance of information is helpting us
- there are many hurdles
- multi-disciplinary efforts are needed.

Chapter 3

“Translation and Convergence for Future Medicine”

- 미래 의학을 위한 중개 및 융합연구
- Asan International Medical Symposium 2016
- Innovative Future for Medical Science & Technology -
- 2016년 6월 17일 (금) 서울아산병원 동관 6층 대강당 외 AIMS

3.1 Plenary Session II “의료기술및 R&D 변화의최신동향”

- Chairperson : 김청수 (서울아산병원비뇨기과교수)

3.1.1 13:30 ~ 14:15 Lecture 1 : 의료분야에서의 빅데이터 : 임상연구 및 진료를 위한 애널리틱스의 활용

- Speaker: David W. Bates (Harvard University, Brigham and Women’s Hospital, USA)
- Rising costs
- Moneyball, Boston red sox, walmart, watson
- Big data 1M - 1giga(human genome) - 1 peta
- EHR, Genetics, Diagnostics, Mobile devices,
- Meaningful Use - EHR - growing.
- https://www.healthit.gov/providers-professionals/meaningful-use-definition-objectives
- https://healthit.gov
- Big data concepts
- Validation is important!
- Big data and research - Brigham and Women’s - Pathology ePath, Immunology Big data Genomic platform
- Essential for future approach
- RPDR - New entity at partners healthcare = CMS, biobank, survey data, imaging, notes repo
- Big data in clinical care
- 5% patients ~ 50% cost
- iCMP claims-based approach - 3000 patients
- multiple parameters - wearable devices - continuous supervision on general care floors
- Adverse events
- PCORnet - not popular
- New Sources - the trajectory of mobile apps

- Literature Review - 7301 titles and abstracts
- App Review - iTunes, Google Play -> possibly useful 16
- Professional Society Review -
- Ginger.io https://ginger.io/
- to drive better health outcomes through the use of passive mobile data and behavioral analytics.
- !!! Example projects - Predictive Modeling
- What we need to do all these
- Analytics tools, repo, data warehouse, epic reporting (Clarity reporting database)
- Clinical data - ubiquitous
- !!!!Novel sources are most likely to provide marginal improvement - social, mobile!!!!
- Predictions / Implications
- Transformative as the internet
- Killer app - Google Maps

3.1.1.1 Questions

- 김규표 교수님 - Social media and health care
- 김청수 교수님 - Government and insurance - reasonably difficult to acquire - costly.

3.1.2 14:15 ~ 15:00 Lecture 2 :합성 항체에서 합성 단백질로

- Sachdev Sidhu (University of Toronto, Canada)
- The Donnelly Centre - From systems biology to systematic treatment
- Therapeutic antibody revolution - highly versatile, numorous diseases
- Ab-durg conjugates, fragment, bispecific, engineered cells
- Targeting cancer with antibodies
- !!! problem - small populations - boutique treatment!!!
- In vitro protein evolution
- Affinity, specificity enhanced
- Antibody molecules
- binding site of Ab
- highly optimized - automatic mutation of binding site
- Toronto Synthetic Antibody Library - highly diverse - Herceptin
- PHAGE - Genentech
- only changed the function, not others
- Functional genomics - **Large-scale, industry-quality Ab generation** - Preclinical biology | The middle was not quite available but now it's doable.
- Cancer Antibody TRAC antibodies - bacerial pathogens
- High yield and high affinity Fabs from naive library - 1394 total against 80 targets
- http://sites.utoronto.ca/sidhulab/about.html
- natural - synthetic Ab - synthetic proteins - synthesizable proteins
- D-protein therapeutics.- samll proteins synthesized entirely rom D-amino acids, Ab like affinity, specificity and stability,
- in vitro d-protein advantages - longer circulating HL than L-proteins - less immunogenicity - ersistant to metabolism in plasma

3.2 Parallel Session I "의료분야에서의빅데이터" Chairperson :김태원 (서울아산병원임상의학연구소장) [대강당]

15:20 ~ 18:00

3.2.1 Lecture 1 : 전자의무기록에 기반한 임상 빅데이터 연구 Alexander Turchin (Harvard University, Brigham and Women's Hospital, USA)

- Data warehouse : integrates data from multiple sources - i2b2 | ABLE | OHDSI
- who entered the data? Wrong input to public repo (DKA for 2 years!)
- Data quality
- Raynaud's syndrome - Omega3 (Failure)

3.2.2 Lecture 2 : 의료분야에서의 빅데이터 분석 Tom Lawry (Microsoft Corp., USA)

- 8 seconds = Concentration time
- Analytics Convergence Zone - Clinical data, Geo/Social/Environmental data/Claims&Cost Data/Pharma&Life Sience Data, Patient & Citizen Data
- https://powerbi.microsoft.com/ko-kr/ !!!!! 반드시 사용해 볼것. 좋은 Visualization.
- http://www.ciokorea.com/news/29118

3.2.3 Lecture 3 : 생물기작 기반 암 오믹스 데이터 분석 기법

- speaker: 김 선 (서울대학교 생물정보연구소)
- https://sites.google.com/site/biohealthinformaticslab/sun-kim
- http://bioinfo.snu.ac.kr/main/index.php
- DNA, RNA, Protein이 중요 - Somatic mutation뿐만 아니라
- Transcriptome (RNA-sequencing data)
- 싸고 쉽다.
- 그에 비해 Underestimated되어 있다.
- Breast cancer
- 가장 잘 알려진 암종.
- 21-gene Oncotype DX !!! http://www.oncotypedx.com/
- PAM50 - Prediction analysis of microarray by 50 gene classifier !!! - Survival 예측하는 Gold-standard
- Transcriptome Data analysis http://prosigna.com/x-us/overview/
- Pathway (context) analysis는 과연 informative한가?
- A Critical Evaluation of Network and Pathway-Based Classifiers for Outcome Prediction in Breast Cancer (PLoS One 2012) http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0034796
- 50개를 랜덤하게 취해도 유의미하게 나왔다. 아무거나 취해도 유의미하게 만들 수 있다. (Negative result!)
- "Based on these results there is currently no reason to prefer prognostic classifiers based on composite features over single genes classifiers for predicting outcome in breast cancer."
- 따라서 50개를 정할 때 기능적인 면을 고려해야 한다.
- PPI-based Pathway Decomposition !!! - 우리의 분류를 기반으로 Survival plot를 그리면 확연한 차이가 난다.
- Decomposed pathway and its activity measurement Using RNA-sequencing data
- 이러한 알고리듬으로 RNA-sequencing data 분석 (1138개의 sample을 사용)
- TCGA data (Breast Cancer)
- 기본적으로 information theory를 응용한 것이다.
- Subtype과 발현량의 ranking에 따라 score를 매긴 후 distinguishing할 수 있다.
- 클래스마다 차이가 확연한 Subnetwork A는 좋은 모델
- 클래스마다 차이가 없으면 Subnetwork C는 나쁜 모델. 우리는 좋은 모델을 택해야 한다.
- **Top10 Regulated pathways by TF/miRNA**
- mir-30a (basal cell cycle activation) -> mir-149, let-7b, mir-30a
- Sub-network mining approach
- Experimental validation requires collaborators who enjoy new approaches.
- 혹시 talk를 들으시고 관심있으면 Contact.

http://aims.amc.seoul.kr/asan/imageDown/homebuilder/20160527?fileName=Scientific-Program-kor.jpg

http://www.amc.seoul.kr/asan/academy/event/eventDetail.do?eventId=572 http://aims.amc.seoul.kr/asan/depts/aims/E/deptMain.do

Chapter 4

ACREP

4.1 Observational Study

- Speaker 이무송

4.1.1 Contents

- Cohort study
- RR

$$\frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

- 단점 - F/U loss, 재발에 대해서 연구 어렵다.
- 연구 대상 수 산출 방법 - Nomogram, 수식적용, 컴퓨터 PASS 2016
- PCORI.org - conduct of Registry
- Cohort는 F/U을 전제로 해서 한다. Retrospective Chart-review

4.2 Observational Study의 Pitfall 및 이를 극복하기 위한 방법

- Speaker: 임영석 교수님

4.2.1 Experimental study? Yes

4.2.1.1 Randomized design? (interventional)- No

- NR CLINICAL trial
- Time series
- PHASE 1

4.2.1.2 Randomized design? (interventional)- Yes

- Clinical Trial
- Community Trial
- Crossover design

4.2.2 Experimental study? No

4.2.2.1 Comparison group? No = Observational study

- Prevalence / incidence,
- time trend,
- case series,
- case reoprt

4.2.2.2 Comparison group? Yes = Analytical study

- Cohort study,
- case-control study,
- cross-sectional study,
- ecologic study,
- PMS
- 두군을 비교하는가 안하는가가 중요한 기준이 된다.

4.2.3 Contents

- research question -(design)- study plan -(implement)- actual study
- findings in the study -(infer)- truth in the study -(infer)- truth in the universe
- 위암, 대장, 폐암 - post op outcome을 통채로 비교하면 안된다.
- internal validity & external validity(generalization)
- PICO anatomy #####
- patient/population/problemn
- Intervention
- Comparison
- Outcome
- Gold standard of clinical studies - RCT
- Sample - randomization (Treated / Control)
- Research question - interesting, important, critical
- Good research question - FINER - Feasible, Interesting, Novel, Ethical, Relevant
- Feasible / Ethical / Relevant 가장 중요한 면
- Prospective Cohort Study -
- Case-control study - 뒤로 간다. 병원에서 case-control 하는 경우는 사망여부. Outcome인 경우가 많다. disease 있고 없고가 아니라.
- 재발에 대한 - 환자군/대조군을 모아서. 그럼 어떻게 대조군 설정한건가?? 이런 것을 정할때 bias가 많이 발생하게 된다.
- Historical cohort - Cohort assembled-(f/u)->Outcome
- 2000-2010 HCC 초치료 근치적 수술적 절제술 받은 환자들의 명단을 확보.
- ITT analysis할때 반드시 필요하다.
- 5년 이상 관찰한 것이 있어.
- Mimic those of clinical trials
- Internal validity를 높여야 한다. restricted cohort / NEJM 2000;342:1887
- IIT 분석을 해라.
- Chance(Random Error) vs Bias(Systematic Error)
- association / cause를 비교해야.
- Confounder
- biasd와는 좀 다르다. 미리 의식하고 물어보기 전엔 절대 알수 없다. 미리 질환에 대해 잘 알고있는 연구자여야만 찾을 수 있다.
- Example : smoking - alcohol - heart disease

- What is the effect of long-term tx(>5y) with a potent oral antiviral agent(entecavir)(I) in patients with chronic hep B(P)
- FDA, 식약처는 Surrogate marker를 가지고 허가를 내준다. (조직학적 개선,) - 이것과 환자의 outcome을 정말로 개선시키는건가? 이건 observational study에서만 찾을 수 있다. historical cohort
- Zero time No treatment control
- Endpoint ascertainment - 재발이 문제가 된다. 무엇으로 재발을 판정할 것인가? MR? CT? 검사간격을 얼마로 했니? 누구도 시비 못할 것으로 outcome measure하는 것이 좋다. (예를 들어 사망의 경우)
- PP vs ITT
- ITT - which treatment option is best at the time decision must be made? - FDA에서 ITT만 인정을 한다.
- Explanatory
- Multivariable Cox PH Analysis - (Event 수를 적어야 한다.) Univariate analysis만으로는 부족.
- Multivariate analysis -
- Propensity score - SPSS로 가능. 양군간 matching - 쌍을 갖춘다. 같은 수로 나온다. 이때는 univariate할 수 있다.
- "consistently observed by unadjusted." - obs study는 의심을 많이 받기 때문에. 이런 분석을 하는 것이 좋다.
- Gadoxetic - liver specific contrast agent
- 2647patients->700명 수술 가능. - surrogate marker - CT에서 못본걸 MR에서 찾았다. | Cost-effectiveness - 무조건 survival. Propensity matching - Inverse Probability Weighing (IPTW)
    1. Unadjsted
    2. mutivariable
    3. IPTW
    4. Propensity
- 제목의 중요성. JCO (IF 21) - Hepatology (IF 11.7) - Gut (IF 14.921) (early rejection so far) - GE (IF 18.187) (accepted with more general terms in the title)

4.2.4 Conclusion

- mimic as closely as possible in RCT

4.3 Diagnostic test & Biomarker Study

- Speaker: 박성호 - 영상의학과

4.3.1 Contents - Diagnostic test

- DTA sutdy
- Prevalence낮으면
- 횡으로 본다. Predictive Value - Prevalence에 영향을 받는다. Pre올라가면 PPV올라가. NPV낮아져.
- odds ratio - prevalence에 영향을 안받는다. intrinsic parameter로 많이 씀.
- case-control study vs cross-sectional study [옛날 용어]
- Cochrane - case-control type accuracy study vs cohort type accuracy study
- NECA - diagnostic case-control study vs diagnostic cohort study
- Area under ROC curve - C statistics
- Youden index - sens spec 더해서 빼기 1 Youden J statistic
- Least Euclidean distance from (0,1) 거리가 최소되는 점. - 쉬운개념
- diagnostic accuracy - 시각적으로 어떻게 구성하는지가 중요함.
- McNemar test
- Comparing two proportions (2x2) - unpaired(fisher,Chi2), paired (McNemar)

4.3.2 Contents - Biomarker

- Biomarker
  - Classifier / Prognostic / Predictive / Monitoring
- Petal et al. MRI-detected tumor response for locally advanced rectal cancer predicts survival outcomes
- Machtay et al. Prediction of survival
  - Prospective
  - S III lung cancer eligible for CCRT
  - Endpoint : overall survival
  - SUV
- Hylton et al.
  - Prospective
  - Index: functional tumor volume measured with pre-surgery breast MRI
  - Comparator: post-surgical pathologic complete response(PCR)
  - Modified C-statistics(ROC) - diagnosis는 있다 없다로 나온다. survival은 time to event - 각각의 time point마다 diagnosis 유사한 통계량이 나와서 그걸 summation
- Studies of predictive accuracy
  - Two approaches - Time-to-event / event by a fixed time
  - Event by a fixed time - Sn Sp ROC - Accuracy study와 유사한 것으로 된다.
- 더 impact있는 것. - randomization을 테스트 후에 할 것인가 아니면 전에 할 것인가? 전에 하는 것이 더 임팩트 있다. 왜냐하면 테스트(+)이면 치료 들어가는 경우가 많기 때문이다.
- 후자에 해당하는 (더 임팩트있는) 스터디의 예.
- Monitoring biomarker
  - Correlation between x and y / delta x and delta y
  - Delta를 보는 것이 중요하다.

4.4 2차 자료원을 이용한 역학 연구군

- Speaker: 예방의학교실/의학통계학과 김화정
- NEJM 2006, BMI and mortality
- 이차자료원 : 특정한 연구목적으로 수집되지 않은 자료
- 공공데이터 - 정부
- 국건영 심평원 자료 - 생각보다 manage하기 쉽지 않다.
- HIRA DB - 건강보험청구자료
- NHISS 국민건강보험자료 공유서비스
- 보건의료 연구에 활용되는 공공데이터
- 장점 : 대규모자료, 장기간 추적관찰. 시간과 비용 절약
- 한국형 - outcomes Research
- NECA에서 자료를 연계해 주겠다 라고 했으나.. 진전이 크지 않음
- 보건의료 빅데이터 개방시스템 - 공공데이터
- 명세서 일반내역 테이블
- 2차자료의 분석은 case-control의 기준 정하기가 어렵다. 금방 분석이 되기 힘듬. Crossvalidation 반드시 해야함.
- 과제신청 - 연구원등록 : 정부3.0에서 검토 자세히 하게됨.
- SAS/R 프로그램.
- 단점 - 5년간의 자료. F/U보기가 힘들어. 진단명의 정확도 문제 - 70%. 에러의 숫자가 클 수 있음.
- 의학통계학과 공공데이터 연구지원 #4639 - 상담, 공공데이터 이용신청, 자료확보, 자료분석, 결과검토
- NHISS 표본연구
- Dramatic decrease in FQ in the pediatric population
- case crossover design
- indication bias - causality - association. confounding by indication

4.5 대규모 이차 자료원을 이용한 clinical prediction model : individual risk/outcome probability 예측 분석법

- Clinical prediction model
- Framingham risk score
- JAMA - moving from clinical trials to precision Medicine, 2016 Apr 26
- DAPT Trial
- Risk for advanced neoplasia and likelihood ratios in each risk group within derivation and validation sets Derivation and validation of a scoring system to stratify the risk of advanced colorectal neoplasia in asymptomatic adults 분자 : 질병있는 / 분모 : 질병없는 - likelihood ratio
- Assumptions for model development - linear regression, Cox proportional hazard regression(Proportionality of hazard ### This should be confirmed.)

	linear reg	logi reg	Cox reg
Overall perf	R2	Nagelkerke r2, brier	the same
discrimination ability	C con-cor-dance stat(AUC)	C stat, time-dependent AUC	Harell C stat, time-dependent AUC
Calibration	Calibration plot, slope	the same as the logistic	the same as the logistic

- C-index 를 사용하여 분석 가능함. C = number of concordant pairs + 0.5/~~
- 새로운 통계 지표. 2가지. NRI - net eclassification improvement
- Korean J Radiol 2016;17(3);339-350 -> predicted probability - 사망할 확률을 계산할 수 있음.
- Framingham그룹에서 발표됨 2008 통계 저널에

4.6 Web-r.org

- Speaker: 문건웅 가톨릭대학교 성빈센트병원 심장내과

4.6.1 Contents

- web-r.org
- 로지스틱 리그레션 - 반응(종속)변수 - 설명변수 . 단변량 분석 먼저 나와 univariate logistic regression
- 다변량 분석.
- 생존분석 - 로지스틱 회귀분석과 비슷한것임. - 다른 것은 시간개념이 들어있는 것임. 얼마 있다가 돌아가셨는지 알 수 있음. KM 분석. cutpoint결정해줌.
- 나무분석 - 생존 나무 분석.
- 진단통계

Chapter 5

Prism

5.1 Morning

5.1.1 Lim Covariate model

5.1.1.1 Ischemic stroke

- Primary endpoint
- time-to-primary endpoint (time-to-event)
- late recurrence, DM
- Secondary endpoint
- late recurrence
- 통상적인 VPC - K-M plots
- Modeling and simulation analysis of the relationship between lesion recurrence on brain images and clinical recurrence in patients with ischemic stroke http://onlinelibrary.wiley.com/doi/10.1002/jcph.427/abstract [Lim and Bae, 2014]

5.1.1.2 MR image -> 예후 예측

- mRS (modified Rankin Scale)
- 응급실에 왔을때
- DM - NIH scale 3D Plot
- 광학영상 - preclinical 에서 부터 NONMEM을 사용해서

5.1.2 FDA - Lee

- http://www.dailypharm.com/News/202010
- Joga Gobburu - 인도사람
- Yaning Wang - deputy director
- Vikram Sinha
- math molecular biology - impressive - reviewer
- Office of CP - 7개 division, 1~5 clinical division- 질환별로 - align (DCP) PM(떠오르는 학문) PG division

5.1.3 Pfizer

- 파리바?
- 크루시파이? - Metz Karlsson과는 아니고..
- 파일러비시니? UW - metrician -> 임상약리에서 뽑았다. (파리바)
- 피터 뮬리건? <-> 아만티아(놀려고 함..)
- 밥 파월 = 임동석 선생님

5.2 PRISM Afternoon

2016.07.12

5.2.1 Kim

- Modeling
- Buzz words
- M&S
- SP&PMx - MBDD - MIDD - MID3 (Drug discovery and deveopment)
- Lean, apply and confirm
- Case I : use of pk modeling in pre-cilnical stage
- NOAEL : Rat 250mg, dog 500mg/kg
- Target exposure
- Questions - have we selected right starting dose? - FDA
- MRSD (FDA guidance) - following actions were taken
- Proposed FTiH dose were 50mg, 100mg~1200mga
- Dose 5-200mg
- MABEL, maybe a challenge but doable with lower s
- NOAEL - MABEL - allometry = we should use all of these.
- Case II : Use of PK in FTiH study Dose Escalation Stage
- Unexpectedly longer half life (x5)
- everything is impacted. POC study
- Questions arose
- Emax model -> nice when it's adhered to the predicted.
- New formulation development
- Case III : Use of PK in FTiH / BIAL lab, BIOTRIAL research site in Rennes, France
- BIA-102474-101 study design
- SAD 8 cohorts
- SAD -> Food effect -> MAD
- What caused these events - threshold, off-target pharmacology, FAAH inhibition
- TSSC report -> Interesting observation related to PK - elimination HL of BIA is gradually extended. Non-proportionality begins.
- Non-proportionality - SAE probability
- Emax model - 80% !!! 50mg QD
- Recommendation : use of sentinel
- London incident, early human (Prediction)
- Summary - PK, PK/PD modeling and simulation is essential

Questions - 20*10 MAD -> okay 50*5 MAD -> not okay, why? - Eye drop -> allometry experience?

5.2.2 Strategic application of PM in global drug development: Experience from Hanmi

- Speaker: Lee Young Mi, Hanmi
- Why do we need PM? - biologically effective dose, earlier translational risk assessment, safety margin(systemic and quantitative translation of animal models to clinic), Pre-clinical modeling to guide clinical dosing, enhancing early stage decision-making, evidence-based decision making and accelerate drug approval
- Systemic and quantitative translational research. PK&PD -> target occupancy, mechanism
- Human PK projections - LAPSCOVERY development strategy
- DRUG+AGLYCOSYLATED FC - Flexible linker
- Longer duration - once weekly, once monthly -> FcRn mediated endothelium recycling / avoiding renal filtration!!!!! - Kidney failure patient can receive the LAPSCOVERY drug. Long-acting protein/peptide
- GLP1, insulin, somatostatin : peptide
- Protein : hGH, IFNa, mG-CSF
- Exendin-4 analog, IFNa -> protein
- LAPSInsulin A (analog of insuling) -> longer HL -> human serum conc vs time profile
- Case 2. Targeted therapy & surrogate PD marker
- It is important to select PD marker!!! Some cancer - hard to choose PD marker. (Eg. Lung ca)
- phosphoEGFR - OLITA (olmutinib) - breakthrough theray designation (FDA) by US FDA - phase II BTD -> modeling when the n= increased??? -> licensed out to Behringer Ingelheim
- Exposure-Response : PK-PD
- Recommended dose selection - CRITICAL!!!
- PK-PD Xenograft
- Targeted therapy & biomarkers - BRAF/KRASmut inhibitor
- Next gen RAF inhibitor(PanRAF) (<-> Classical RAF inhibitor = rebound MAPK reacitivation)
- Methods difference (pMEK), (pERK) -> aided dose seletion (lower exposure and the same PD marker)
- HM95573 and Cobimetinib in MAPK activated HCC cell lines
- combination -> can lower dose

5.2.3 MBDD

- Speaker: Lim
- MBDD (Learn & confirm cycle) course run
- Information management tool = Modeling
- Quantitative information (GO/NO-GO decision)
- Various and diverse information
- Quick win, fast fail - PK/PD modeling and simulation
- Abundance of drug discovery - preclinical development (Mechanism-based biomarker, imaging biomarker) - accelerated PoC (IIb/IIa) - confirmation, dose finding
- System-specific parameters, drug-specific parameters, structural model
- Extrapolation
- Quantify the exposure in remote and/or inaccessible
- Allometry vs PBPK
- assumes that the nly diff between human and the other mammals is size = imprecise, mono-exponential elimination
- DHP107 - IV paclitaxel
- 480mg/m2 was the most common MTD(Maximal Tolerability Dose) in virtual phase 1 trial for DHP107
- Case II - Ticagrelor PD
- ticagrelor and AR-C124910XX
- Maximal platelet aggregation
- Case III - Early characterization of an antibiotics using bacterial time kill assays and human PK study
- Preclinical PD + Human PK => Predict human PD

- Monte-Carlo simulation using PK/PD model
- Case IV - integrative PK/PD Model
- 16182HanLimPyung441) - MFDS
- Integrative, mechanistic PK/PD model
- Tumor size

Questions - NONMEM -> PBPK? ADAPT?(Program?) - THETA, ETA (60-70) Generally 40

5.2.4 Pharmacometric information in drug label

- Speaker : Bae
- Ocaliva (obeticholic acid tablets)
- oral use | initial U.S. Approval 2016.05.27 - FXR agonist - Tx of PBC - Omega matrix -> POPPK analysis
- NUPLAZID (pimavanserin)
- Parkinson's ds psychosis
- Oral
- POP modeling 구체적목적
- fixed effects covariate 찾는다
- interintra subject random variability의 크기를 평가
- 개인별 pk,pd
- 농도, 폭로, 반응/효과, 유해반응 simulation하기 위한 모형을 구축
- Total variability
- Fixed portion + random portion
- fixed effect = explainable
- Eta (interindividual (random) variability)
- NONMEM
- F = function of (theta, , covariates) # Fixed
- Y = function of (F, epsilon) # eta=0(무시)하면서 예측한경우 = Typical prediction
- theta = constant, nu~MVN(0,omega), eta~MVN(0, sigma) 확률변수
- Covariates - usually dose, time, demographics and other measurement
- Epsilon = express homoscedastic, proportional, exponential or combined errors
- Dose,time = covariate (statistics)
- Eta - Realized Eta = 0이 아닌 숫자화된 Eta (inter individual)고려해서 한거 - F:IPRE F:PRED(Typical prediction)
- Population Concept
- Eur J Pediatr(2015) 174:1671-8 Prediction of plasma caffeine concentrations in young adolescents following ingestion of caffeinated energy drinks: a Monte Carlo simulation - [Lee et al., 2015]
- CL, Vd(실제론 둘이 연관이 있다.) -> Correlation을 유지한 채로 sampling 되도록. MVN
- Pharmacometric Review : pop PK-PD model

- Visual Predicted Check
- Prediction band

  The fast-growing consumption of caffeinated energy drinks (CEDs) is linked to increasing reports of caffeine intoxication in adolescents. There is limited data available regarding plasma caffeine concentrations in this population after CED intake and the potential implications for caffeine-related toxicity. This study was an in silico population pharmacokinetic analysis of caffeine. Population pharmacokinetic model of oral caffeine was derived from a previous study of healthy male volunteers. Maximal plasma caffeine concentration (C max) profiles following ingestion of one or two servings of popular CEDs were predicted using Monte Carlo simulation and available population body weight data of 10–15-year-old Korean adolescents. Caffeine C max values were positively correlated with the amount of caffeine ingested in CEDs and negatively correlated with body weight. The median (range) C max profiles varied from a low of 1.2 (0.5–2.6) mg/L to a concentration that is potentially associated with harmful caffeine-related effects of 25.4 (8.1–55.6) mg/L. A subgroup of female 10–11-year-old subjects exhibited the highest caffeine exposure profiles. Conclusion: These data indicate that CED ingestion can increase the risk of serious caffeine intoxication in young adolescents, particularly those with low body mass.

5.2.5 Pharmacometrics in Dose Optimization

- Speaker : Lee, FDA
- Interindividual variability (PD, PK)
- Secukinumab (Cosentyx) - target population
- https://en.wikipedia.org/wiki/Secukinumab (Novartis)
- Example of dose optimization
- IL-17(A) - Etanercept, infliximab, adalimumab(humira, shallow), ustekinumab = biologics
- 몸무게 크면
- IgA, 4 Phase III, (2 of them were pivotal study)
- PMC - post marketing commitment
- the higher conc. => the higher incidence of infections (tolerable)
- Edoxaban (흥미로운 약물)
- NOAC - New Oral Anti-coagulants (4th)
- 1st rivaroxaban, 2nd dabigatran(issue-EMA), 3rd apixaban
- Ace Meeting?
- Normal - Mild - Moderate
- Exposure - response relationships (Efficacy-Stroke, safety-bleeding)
- Benefir-risk relationship is not novel. (Dabigatran: RE-LY trial)
- exposure-response relationship PK matching.

```
## Writing 2 Bibtex entries ...

## OK
## Results written to file 'References.bib'
```

Bibliography

Jung Woo Lee, Yookyung Kim, Vidya Perera, Andrew J. McLachlan, and Kyun-Seop Bae. Prediction of plasma caffeine concentrations in young adolescents following ingestion of caffeinated energy drinks: a monte carlo simulation. *European Journal of Pediatrics*, 174(12):1671–1678, jun 2015. doi: 10.1007/s00431-015-2581-x. URL http://dx.doi.org/10.1007/s00431-015-2581-x.

Hyeong-Seok Lim and Kyun-Seop Bae. Modeling and simulation analysis of the relationship between lesion recurrence on brain images and clinical recurrence in patients with ischemic stroke. *The Journal of Clinical Pharmacology*, 55(4):458–466, dec 2014. doi: 10.1002/jcph.427. URL http://dx.doi.org/10.1002/jcph.427.