<img src="http://ibuildapp.s3-website-us-east-1.amazonaws.com/assets/data/02618/2618739/apps/2751115/27734317/745260396543325.jpg" style="font-family: "PT Sans Caption", sans-serif;" width="650"> Once protocol get Asia Open Health Care Data Protocol send chronic disorders index to standard platform to distribute blood composition index whether this is possible status of high chronic disorders and any other medical condition. The standard to make a diagnosis about chronic disorders index is combination of computerized diagnosis and diagnosis from medical providers. Then, users can use the combined standard which is much more improved and advanced to make a diagnosis. intelligent standard about chronic disorders can create new standard about new disorder by using statistics.
   Manual standard about chronic disorders can be updated from medical provider. From each health care centers such as public health center, university hospital and any other health care center associated with national health insurance in Republic of Korea because the medical provider of each health care center are certificated from ministry of health and welfare properly. So, to make a diagnosis by using both of intelligent standard and manual standard can be dealt with confidently.   One of the most important and valuable things on this research is new standard can be created by using statistical hypothesis testing to make a diagnosis with standard. In statistical hypothesis testing, the <span lang="EN-US" style="font-family:한

컴돋움;mso-ascii-font-family:한컴돋움
;mso-font-width:100%;letter-spacing:0.0pt;mso-text-raise:0.0pt;font-style:italic;">p-value is the probability for a given statistical model that, when the null hypothesis is true, the statistical summary (such as the sample mean difference between two compared groups) would be the same as or more extreme than the actual observed results.
 Major take home messages:<o:p></o:p> <ul style="margin-top:0cm" type="disc">

<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">Gene mutations analysis (genomics) plays an important role in the diagnosis and screening of monogenetic inherited metabolic liver diseases (e.g., hemochromatosis, Wilson's disease) and frequently replaces more invasive procedures in daily clinical practice<o:p></o:p>

<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">Penetrance of mutations can be highly variable and unpredictable limiting the use of mutation screening in clinical practice (e.g., hemochromatosis)<o:p></o:p>

<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">The plethora of possible gene mutations can limit the practical use of mutation analysis for diagnosis of inherited metabolic liver diseases (e.g., Wilson's disease, alpha-1-antitrypsin deficiency)<o:p></o:p>

<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">Genotype-phenotype correlations are often disappointing (e.g., Wilson's disease)<o:p></o:p>

<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">These limitations are due to a

lack of information on other genetic and environmental factors<o:p></o:p>
<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">Postgenomic tools and a systems biology approach could overcome these limitations by providing and linking additional information at the mRNA, protein and functional levels (transcriptomics, proteomics, metabolomics); currently, however, such approaches are limited to research<o:p></o:p>
<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">Multifactorial (oligo- or polygenetic) metabolic and cholestatic liver diseases (e.g., NAFL/NASH, acquired cholestatic disorders) still rely on classic phenotypic diagnostic criteria in daily clinical practice<o:p></o:p>
<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">In the future, postgenomic analysis of body fluids (e.g., serum) and/or liver tissue could be helpful in predicting prognosis and individualizing pharamacological as well as dietary treatment of metabolic and cholestatic liver diseases <o:p></o:p>
<li class="MsoNormal" style="margin-right:36.0pt;text-align:justify;text-justify:inter-ideograph;mso-list:l1 level1 lfo1;tab-stops:list 36.0pt">Gene therapy of metabolic and cholestatic liver diseases is in its infancy and current gene therapy is primarily experimental, most human clinical trials being only in the research stages <o:p></o:p>
   1. Introduction: present and future role of postgenomic approaches to metabolic liver diseases<o:p></o:p> Metabolic liver disease represent a
suitable area for the clinical application of genomics and postgenomics since these diseases are frequently caused by a mutation of a single gene which results in a functional/metabolic phenotype (e.g., hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency). The task is more complex in multifactorial, oligo-/polygenetic

diseases (e.g., alcoholic and non-alcoholic fatty liver disease ((N)AFL) / steatohepatitis ((N)ASH), acquired cholestatic disorders). In the post-genomic era, the focus has shifted to an integrated approach ("functional genomics") and transcriptomics, proteomics and metabolomics (Table 1) as classical postgenomic tools which can also be applied to metabolic and cholestatic liver diseases (1-3). Such comprehensive approaches to biology can be characterized as "omic" research in which one generates large resources of information on biologic molecules in aggregate without necessarily knowing in advance which pieces of information and which correlations will prove most important. Historically, "omics" began with genomics and the Human Genome Project (1,2).<o:p></o:p>   Transcriptomics describes the transcriptional (mRNA) patterns caused by metabolic liver diseases in a genome-wide range (Table 2). Such expression patterns can be identified using gene expression profiling techniques like DNA- or oligonucleotide microarrays which allow to systematically determine the mRNA expression level of practically every gene of an organism (1). Oligonucleotide microarrays can not only be used for gene expression profiling studies, but also for mutation detection and/or polymorphism screening. <o:p></o:p>   Table 1: Paradigm Shifts for Metabolic Liver Diseases in the Postgenomic Area <o:p></o:p> <table class="MsoNormalTable" border="1" cellspacing="0" cellpadding="0" style="border: none;">
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<span
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Diseases<o:p></o:p>
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genomics<o:p></o:p>
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genomics<o:p></o:p>
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Genomics<o:p></o:p>
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Transcriptomics,
proteomics, metabolomics<o:p></o:p>
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Genetic mutation
analysis supplemented by mRNA, protein and metabolite profiling from body
fluids (serum) or diseased liver tissue<o:p></o:p>
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Monogenetic
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Multifactorial
disorders<o:p></o:p>
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Hemochromatosis,
Wilson's, alpha-1-antitrypsin deficiency versus (N)AFL/(N)ASH,
acquired (e.g., drug-induced) cholestasis <o:p></o:p>
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Specific DNA diagnosis<o:p></o:p>
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Monitoring of
susceptibility<o:p></o:p>
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Penetrance of
mutations, genotype-phenotype correlations (e.g., hemochromatosis, Wilson's), prediction of
drug side effects, tolerance for alcohol and diets<o:p></o:p>
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Etiology (specific mutation)<o:p></o:p>
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Pathogenesis (mechanism)<o:p></o:p>
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Gene action<o:p></o:p>
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Gene regulation<o:p></o:p>
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Analysis of one
gene<o:p></o:p>
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Analysis of
multiple genes in gene families, pathways, systems<o:p></o:p>
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Microarrays,
multiplex PCR for detection of several mutations, disease modifying genes<o:p></o:p>
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Peltonen & McKusick, Science
2001; 5507: 1224-1229 <o:p></o:p> <span

lang="EN-GB"> Proteomics permits to visualize the protein
content of the liver and serum (or other body fluids) under certain diseases conditions (Table 2). The dynamic nature of the proteome of a cell or a tissue in metabolic liver diseases provides ample justification for studying gene expression directly at the proteomic level. Proteomics allows the qualtitative and quantitative assessment of protein patterns, including postranslational protein modifications (e.g., phosporylation, glycosylation) associated with a disease (2,3). Some metabolic liver diseases such as alpha-1-antitrypsin deficiency (AATD) are paradigm protein (misfolding) diseases which can be efficiently addressed at the protein level. Abnormal protein patterns can also be a consequence rather than cause of the disease. In addition to simple, conventional techniques such as serum electrophoresis ("poor man's crude proteomics") and isoelectric focusing or serum proteins (e.g., Pi type in AATD), a combination of seperation techniques for proteins (e.g. liquid chromatography, 2D gel electrophoresis) with mass spectrometry could be a highly sensitive analytical tool for metabolic liver diseases. New techniques such as electrospray ionization and matrix-assisted laser desorption-ionization (MALDI) have enabled the transfer of proteins in the gas phase and their characterization by mass spectrometry as rapid and high throughput technology. This approach can identify differentially expressed proteins in comparison to healthy tissue/body fluids and identify new proteins as biomarkers, clues for pathogenesis and potential drug targets in metabolic liver diseases. The release of quantitatively and qualititively altered hepatic proteins from diseased hepatocytes (or other liver cells) into the serum may allow a non-invasive monitoring of liver expression profiles. Some principles of proteomics are already "applied" in a small scale in everyday clinical practice (Table 2). Of course the sensitivity of such methods has to be much higher than routine biochemical methods, since the pathophysiologically altered proteins not necessarily are the most abundant ones (e.g. MPLC-ion trap mass spectroscopy for detection of low abundance plasma proteins) (1-3).<o:p></o:p> <span lang="EN-GB" style="font-size:10.0pt;
mso-ansi-language:EN-GB"><o:p> </o:p> <span lang="EN-GB" style="font-size:10.0pt;
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DNA<o:p></o:p>
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Sequencing<o:p></o:p>
PCR-based mutation
analysis (including multiplex PCR) <o:p></o:p>
Oligonucleotide
arrays<o:p></o:p>
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Diagnosis and
screening of monogenetic diseases (e.g., hemochromatosis, Wilson's)<o:p></o:p>
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RNA<o:p></o:p>
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cDNA/oligonucleotide
microarrays<o:p></o:p>
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Analysis of liver
biopsies (complex multifactorial diseases)<o:p></o:p>
<o:p> </o:p>
Possible use for
mutation screening (DNA from peripheral blood leukocytes)<o:p></o:p>
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Proteomics<o:p></o:p>
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Protein<o:p></o:p>
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2 D Elphor<o:p></o:p>
Mass spectroscopy
(MALDI-TOF-MS,<o:p></o:p>
SELDI-TOF-MS, ESI-MS)<o:p></o:p>
Protein chips<o:p></o:p>
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Analysis of liver
biopsies (complex multifactorial diseases)<o:p></o:p>
<o:p> </o:p>
Serum markers of
disease (e.g. alpha-1-antitrypsin Pi phenotype)<o:p></o:p>

<o:p> </o:p>
Detection of disease-associated posttranslational protein modifications (e.g., carbohydrate deficient transferrin)<o:p></o:p>
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Metabolomics<o:p></o:p>
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Metabolic products (low-molecular-weight)<o:p></o:p>
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Chromatography <o:p></o:p>
High resolution NMR spectroscopy<o:p></o:p>
Mass

spectroscopy<o:p></o:p>
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Phenotypic screening and diagnosis<o:p></o:p>
<o:p> </o:p>
Detection of abnormal metabolites in inherited pediatric liver diseases<o:p></o:p>
<o:p> </o:p>
Monitoring of drug (side) effects<o:p></o:p>
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“Clinomics”<o:p></o:p>
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Clinical patient

data<o:p></o:p>
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History taking<o:p></o:p>
Physical
examination<o:p></o:p>
Routine clinical
chemistry<o:p></o:p>
Imaging studies<o:p></o:p>
Cytology/histopathology
<o:p></o:p>
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Current clinical
routine<o:p></o:p>
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Bioinformatics<o:p></o:p>

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Data generated by
genomics, proteomics, metabolomics and “clinomics”<o:p></o:p>
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Data bases<o:p></o:p>
Bioinformatical
tools<o:p></o:p>
Cyberspace<o:p></o:p>
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Data analysis,
mining, integration and interpretation<o:p></o:p>
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</tbody></table> Abbreviations: ESI,
electron spray ionization, MALDI-TOF, matrix-associated laser
desorption-ionization time of flight; MS, mass spectroscopy; SELDI-TOF, surface enhanced laser desorption-ionization
time of flight, <o:p></o:p> <p class="MsoNormal" style="mso-margin-top-alt:auto;margin-right:3.5pt;
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n lang="EN">Metabolomics</i>, or metabolic profiling, is concerned with the
measurement of global sets of low-molecular-weight metabolites to detect changes in cell behavior and organ function (Table 2). The term ‘metabolome’, like ‘genome’ or ‘proteome’, refers to the <u>complete</u> set of metabolites found
in an organism (1). Metabolomic approaches use high throughput analytical techniques such as chromatography, NMR spectroscopy and mass spectroscopy to measure populations of low-molecular-weight metabolites in biological samples. These large-scale efforts involve the identification and quantification of known and also yet <u>unknown</u> metabolites in human tissues and fluids. Metabolite profiles can be important indicators of pathological states and raise the possibility of identifying novel surrogate markers of disease.
Intuitively, one might think that metabolomics is largely the domain of metabolic (liver) diseases. Certainly, “focused” metabolic profiling is already performed in (mainly pediatric, congenital) metabolic defects (e.g., screening for abnormal fatty acid metabolites in fatty acid oxidation defects; bile acid metabolites in bile acid synthesis defects). However, phenotypic/metabolic “work-up” and diagnosis of metabolic liver diseases does not necessarely require complete and complex metabolic profiles. For example “simple” determination of hepatic iron and copper concentrations may give an adequate diagnosis of hemochromatosis and Wilson’s, respectively. Rather, metabolomics could provide additional information on the metabolic consequences (“metabolic footprint”) of the liver disease (e.g., induced by iron and copper overload) and could thus provide potential prognostic information. Thus, metabolic profiling is not restricted to metabolic liver diseases and may not only have a significant impact on the diagnosis, but also on prediction, prevention and monitoring of diseases. Moreover, monitoring of hepatic adverse drug reactions may provide a better understanding of individual sensitivities to prescription drugs.<o:p></o:p> Recently the term “clinomics” has been coined (Table 2)
to emphasize the complexity and large amount of data generated in every day clinical practice by history taking, physical examination, routine clinical (bio)chemistry, imaging studies and pathology (cytology histology). Again, “-omics” in clin-omics principally refers to a “holistic” approach (e.g., whole body scans etc.). Physical examination of a patient may also be considered a system(at)ic and therefore holistic approach. Naturally, such clinical data have to be integrated with (post)genomic data for obtaining clear molecular-clinical correlations with potential clinical (diagnostic,

prognostic, therapeutic) relevance.<o:p></o:p> The challenge lies in the elucidation of the large amount of information generated by genomics, transcriptomics, proteomics and metabolomics by appropriate bioinformatics tools and data processing, as well as giving a biological meaning to the obtained data. Advanced statistical and bioinformatic tools have to be employed to maximise the recovery of information and interpret the large datasets that are generated. Data integration can combine metabolite analysis and gene expression profiles in complex, multifactorial diseases and thus identify perturbed key metabolic pathways. Currently such approaches are still restricted to research applications. Ongoing research projects should however provide us with all the necessary information to make clinically relevant predictions based on expression and metabolic profiles in the near future.<o:p></o:p> Pharmacogenomics and nutrigenomics are two specific examples for the application of the recent progess in (post)genomics. Both may be particularly relevant for the prevention and treatment of metabolic, cholestatic and toxic liver disease, including drug side-effects. Pharmacogenomics is the study of how an individual's genetic inheritance affects the individual response to drugs and holds the promise that drugs might one day be tailored for individuals and adapted to each person's own genetic makeup. This approach should not only result in more powerful medicines targeted to specific diseases but is also expected to reduce drug side effects, especially when combined with metabolomics (4,5).<o:p></o:p> Nutrigenomics is the study of how different nutrients can interact with particular genes to increase the risk of metabolic (liver) diseases (6-8). The nutrition-health relationship depends on the

adaptive capacity of genes in response to the diet consumed. Several mechanisms can modify gene performance and epidemiological studies have reported that early-life metabolic imprinting occurs in man. Naturally, nutrigenomics may be particularly relevant for understanding and managing (N)AFL/(N)ASH. Alcoholomics
is another emerging subdiscipline with relevance to hepatology.<o:p></o:p> <span lang="EN-GB" style="font-size:10.0pt;
mso-ansi-language:EN-GB">Table 3. Examples for Monogenetic Liver Diseases of Interest for the Clinical Hepatologist <o:p></o:p> <table class="MsoNormalTable" border="1" cellspacing="0" cellpadding="0" width="614" style="width: 460.5pt; border: none;">
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Hemochromatosis<o:p></o:p>
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HFE<o:p></o:p>
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Increased
intestinal iron absorption, iron overload<o:p></o:p>
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Low penetrance of
mutations in screening populations<o:p></o:p>
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Alpha-1-Antitrypsin (AAT) Deficiency <o:p></o:p>
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AAT<o:p></o:p>
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Hepatic accumulation of misfolded AAT leading to hepatocellular injury<o:p></o:p>
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Phenotypic screening (AAT phenotyping) clinically more relevant<o:p></o:p>
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Wilson’s <o:p></o:p>
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ATP7B1<o:p></o:p>
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Defective biliary copper excretion, copper overload<o:p></o:p>
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Large number of possible mutations restrict the clinical use of mutation screening, poor genotype-phenotype correlations<o:p></o:p>
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Progressive Familial Intrahepatic Cholestasis (PFIC)<o:p></o:p>
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Various
hepatobiliary transporters (FIC1, BSEP, MDR3) <o:p></o:p>
PFIC-1 (FIC-1)<o:p></o:p>
PFIC2 (BSEP)<o:p></o:p>
PFIC-3 (MDR3)<o:p></o:p>
Bile acid
synthesis defects<o:p></o:p>
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Cholestasis,
PFIC-1 with exrahepatic manifestations (pancreatitis, diarrhea)<o:p></o:p>
PFIC-3 with bile
duct injury<o:p></o:p>
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Mutation
screening not routinely available (research setting)<o:p></o:p>
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Benign Recurrent Intrahepatic Cholestasis (BRIC)<o:p></o:p>
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Hepatobiliary transporter genes (FIC1, BSEP), “milder” defects <o:p></o:p>
BRIC-1 (FIC-1)<o:p></o:p>
BRIC2 (BSEP)<o:p></o:p>
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Intermittent episodes of cholestasis and pruritus<o:p></o:p>
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Poor genotype-phenotype correlations (same mutation sometimes found in both BRIC and PFIC)<o:p></o:p>
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Cystic fibrosis<o:p></o:p>
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CFTR<o:p></o:p>
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Cholestasis, focal
biliary cirrhosis, sclerosing cholangitis<o:p></o:p>
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Dubin-Johnson<o:p></o:p>

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MRP2<o:p></o:p>
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Jaundice,
defective biliary excretion of conjugated bilirubin<o:p></o:p>
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Crigler-Najjar<o:p></o:p>
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Jaundice,
defective bilirubin conjugation<o:p></o:p>
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Mutation
screening not routinely available (research setting)<o:p></o:p>
</td>
</tr>
</tbody></table> <o:p> </o:p> 2. What the clinician asks of postgenomics for the management of (inherited) metabolic and cholestatic liver diseases<o:p></o:p>   The usual clinical setting:<o:p></o:p> Genomics and postgenomics could
principally play a role in the diagnosis, prognosis, monitoring and therapy of metabolic and cholestatic liver diseases. The usual clinical setting for the diagnosis of metabolic liver disease is a patient after exclusion of hepatitis B and C when the question arises whether he/she could have a monogenetic disorder such as hereditary hemochromatosis, alpha-1-antritrypisn deficiency, Wilson's disease or a multifactorial/polygenetic disease such as NAFL/NASH (Table 3 and 4). Screening of relatives or individuals of high risk group is another practical scenario. Moreover, the patient may present with an "unusual" clinical presentation, where a "rare" metabolic and inherited diseases is considered (Table 3). This scenario may be more common in the pediatric liver

clinic. Table 3 lists some of the relevant monogenetic diseases, Table 4 some of the most important multifactorial (polygenetic) diseases. <o:p></o:p> <span lang="EN-GB" style="font-size:10.0pt;
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mso-ansi-language:EN-GB">Table 4: Multifactorial Metabolic and Cholestatic Diseases with Potential Genetic Background <o:p></o:p> <table class="MsoNormalTable" border="1" cellspacing="0" cellpadding="0" style="border: none;">
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  <p class="MsoNormal" style="margin-left:18.0pt;text-align:justify;text-justify:
  inter-ideograph">Disease<o:p></o:p>
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  <span lang="EN-GB" style="font-size:10.0pt;
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  inter-ideograph"><span lang="EN-GB" style="font-size:10.0pt;mso-ansi-language:
  EN-GB">NAFL/NASH<o:p></o:p>
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Mediators and regulators of inflammation, oxidative stress, cytokines, metabolic enzymes<o:p></o:p>
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AFL/ASH<o:p></o:p>
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Same as NAFL/NASH (including alcohol metabolism)<o:p></o:p>
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Acquired (e.g. drug-induced cholestasis)<o:p></o:p>
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Hepatobiliary
transporters (BSEP, MRP2), phase I and II enzymes involved in drug metabolism
and detoxification (CYPs) and transport (MDR1, MRPs)<o:p></o:p>
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EN-GB">Intrahepatic cholestasis of pregnancy<o:p></o:p>
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Hepatobiliary
transporters (MDR3, BSEP, MRP2), sex hormone metabolism<o:p></o:p>
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inter-ideograph"><span lang="EN-GB" style="font-size:10.0pt;mso-ansi-language:
EN-GB">Sclerosing cholangitis<o:p></o:p>
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Hepatobiliary
transporters (CFTR, MDR3), inflammation and cytokine genes<o:p></o:p>
</td>
</tr>
</tbody></table> <o:p> </o:p> Current clinical reality:<o:p></o:p> Currently, (post)genomic approaches
mainly play a role for diagnosis and screening of metabolic liver diseases. The principal question is whether to approach the disease phenotypically or genetically. Both approaches are not mutually exclusive (e.g. mutation analysis following a phenotypic screening test). Monogenetic diseases are the domain of mutation analysis, while genetic tests so far have no routine diagnostic relevance in polygenetic/multifactorial diseases. Genetic diagnosis frequently has already replaced phenotypic (confirmation of) diagnosis in monogenetic metabolic liver diseases. The clinician not only has to know which test to order, but also where to send it, the latter being sometimes a fastidious ask for “rare” diseases where a nearby reference lab may be difficult to find. Another problem is the (lack of) reimbursement by insurances for shipping, material and personel costs associated with molecular analysis outside of clinical routine. Unfortunately, mutation analysis is often complicated by the fact that there is a plethora of possible mutations (e.g. Wilson’s) or the diagnostic test is not established and only performed under “research conditions” (e.g. certain cholestatic syndromes). Moreover, genotype-phenotype correlations are often problematic and the penetrance of an identified mutation may vary greatly which may be problematic when a mutation has been identified in a screening setting. For multifactorial diseases, the practical relevance of mutation analysis of single genes or small groups of genes (e.g., modifier genes) is not yet established but offers promise for the future. Multiplex PCR may be a means to simultaneously and rapidly asses groups of relevant (functionally/pathogenetically linked) genes. Postgenomics tools (transcriptomics, proteomics, metabolomics)

are still restricted to the research setting, but could provide important prognostic and therapeutic information for the management of monogenetic and polygenetic metabolic liver diseases in the future. In daily clinical practice, the diagnosis of metabolic liver diseases is reached by clinical, biochemical and in some instances also histological means which are supplemented and confirmed by the use of appropriate genetic tests. Phenotypic diagnosis and screening for metabolic liver diseases in adults relies on “simple” routine biochemical parameters and not on sophisticated metabolomics methods such as NMR or mass spectroscopy. Future systems biology approaches are still far away from clinical reality, but may be helpful for individualizing diagnosis, prognosis and therapy.<o:p></o:p>

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What the clinician asks for:<o:p></o:p> The clinician asks for a fast,
reliable and uncomplicated method, ideally a non-invasive “one stop shopping” test providing all the relevant diagnostic, prognostic and therapeutic information. Ideally this would mean drawing blood and send it to a
(post)genomics lab. There, it is passed through a mass spectrometer for protein analysis and cross-referenced to the DNA profile. This approach should allow hundreds of normally
expensive and time-consuming medical tests to be performed within a short amount of time. Ideally, the result comes back a few days later. It is predicted that these new tools may shorten diagnosis time by a factor of 100 and reduceoverall testing costs by a factor of
1000 or more. Alternatively this could also mean putting the entire

patient into a scanner to obtain his/her metabolic profile (e.g., by NMR spectroscopy). In addition, mRNA and protein gene expression profiles could be obtained from a routine liver biopsy. These approaches should give not only give diagnostic, but also prognostic and therapeutic information in the sense of a tailored drug therapy and diet recommendations (“individualized medicine”) (14). <o:p></o:p>   Table 5: What the Clinician Does and Does Not Want from Postgenomics<o:p></o:p> <table class="MsoNormalTable" border="1" cellspacing="0" cellpadding="0" style="border: none;">
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Wanted<o:p></o:p>
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Unwanted<o:p></o:p>
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Easily accessible, fast and standardized tests<o:p></o:p>
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Long waiting time, searching the internet and calling around were to send a sample, non-standardized test conditions<o:p></o:p>
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Tests from routinely acquired blood and (paraffin-embedded) liver samples (urine for some diseases)<o:p></o:p>
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Tests from difficult-to-obtain tissues and body fluids, complicated sample processing and storage prior to analysis (interfering with clinical routine procedures)<o:p></o:p>
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Result helpful for making/confirming the diagnosis<o:p></o:p>
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Unclear
diagnostic relevance of result<o:p></o:p>
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Prognostic and
therapeutic implications, prediction of spontaneous clinical course and
response to therapy (including side effects)<o:p></o:p>
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Unclear
prognostic and therapeutic implications<o:p></o:p>
</td>
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</tbody></table> <o:p> </o:p> Disease specific considerations:
present and future<o:p></o:p>   Hemochromatosis: Two common HFE mutations (C282Y and H63D), have been described.
Approximately 85-90% of patients with typical clinical manifestations of hereditary

hemochromatosis are homozygous for C282Y, although compound heterozygosity (i.e., carrying two different mutations: C282Y/H63D) may also result in the disease (9,10). Other HFE mutations (e.g., S65C) have also been described which are clinically less important, but can lead to mild iron overload when inherited in the compound heterozygous state with C282Y or H63D. Although the majority (90% of men, 70% of women) of C282Y homozygotes develop increased body
iron stores, end-organ damage occurs much less frequently than previously thought (9,10). Recent data suggest that the homozygous hemochromatosis mutation (C282Y) is associated with low penetrance and mild expressivity when identified in population screening studies (10-20%, in some studies even <1%). Both genetic and environmental factors (diet, alcohol use) and gene-gene interactions may modify disease expression and influence the penetrance (9). Based on these difficulties, genotypic-based screening strategies are problematic and points toward the need for a systems biology approach. Phenotypic screening of adults using transferrin saturation and serum ferritin levels identifies the majority of individuals who develop iron overload. HFE genotyping, when combined with serum biochemical measurements, has reduced reliance on liver biopsy as a diagnostic tool. Complex metabolic screening in the sense of “metabolomics” is not routinely necessary, since the pathophysiological consequences are easily detectable with routine tests (e.g. serum and liver iron studies). However, gene expression profiles from liver biopsies and metabolic profiles from serum could be useful in assessing the neoplastic risk of patients with hemochromatosis and the potential for reversal of liver fibrosis/cirrhosis. Of course, this could generally apply to any liver disease.<o:p></o:p>   Wilson's disease: Since none of the commonly used parameters alone allows the diagnosis
with a sufficient degree of certainty, a combination of various parameters is necessary to firmly establish the diagnosis (11). Mutation analysis of the Wilson’s gene (ATP7B1) for diagnosis is complicated by the large number of different (>200) mutations, each of which is rare. In addition, most patients are compound heterozygotes which further complicates genetic diagnosis. In line with the “lessons from hemochromatosis” (9) several new genes involved in copper metabolism have been discovered which may complicate mutation analysis even further. In a diagnostic setting, direct mutation analysis is only helpful if a mutation occurs with a reasonable frequency in the general population. The most common mutations in Europe are: H1069Q (allele frequency

44%), mutations of exon 8 (7%), 3400delC (3%) and P969Q (2%) (11). The pattern of mutations differs in other parts of the world. A multiplex polymerase chain reaction for the most frequent Wilson's disease mutations in the geographic region may become a feasible diagnostic approach. Highly polymorphic microsatellite
markers flanking the Wilson's disease gene may allow a genetic defect to be traced in a family by haplotype analysis (11). However, at least one first-degree relative and the index patient are required for haplotype analysis. Again, the metabolic defect itself (copper overload) is fairly “simple” and does not routinely require complex metabolic screening. However, proteomics and metabolomics could assess the individual consequences of copper toxicity.<o:p></o:p>   Alpha-1-Antritrypsin deficiency (A1ATD): Phenotypic screeining and diagnosis (Pi
phenotype determined by isoelectric focuing) still dominates over genetic approaches, since the abnormal protein of interest is easily detectable and accessable in the serum (12). A1ATD
could become a paradigm disease for proteomic studies.<o:p></o:p>   Cholestastic syndromes: Several monogenetic, hereditary cholestatic syndromes now can be
attributed to specific mutations of individual hepatobiliary transporter genes (Table 3) (13,14). Examples include progressive familial intrahepatic cholestasis (PFIC 1-3), benign recurrent intrahepatic cholestasis (BRIC1-2), Dubin-Johnson syndrome and liver involvement in cystic fibrosis. Incomplete or heterozygous transport defects may predispose to acquired cholestatic liver injury (e.g., subtypes of intrahepatic cholestasis of pregnancy, drug-induced cholestasis, sclerosing cholangitis) (Table 4). Exposure to acquired cholestatic injury (e.g., drugs, hormones, proinflammatory cytokines, biliary obstruction or destruction) can also result in altered expression and function of hepatic uptake and excretory systems, changes which may maintain and contribute to cholestasis and jaundice. Drug-side effects could become an area of application for pharmacogenomics and toxicogenomics. Transporter polymorphisms of the main hepatobiliary export systems do not appear to play a major role in the pathogenesis of PBC, but MDR3 and CFTR defects could be involved in the pathogenesis of subgroups of PSC. Genetic analysis of

transporter genes is not routinely available. Immunohistochemical staining of transporters in liver biopsies may at least in part allow a qualitative assessment (presence or absence of transporters, mislocalization). Postgenomics could help to identify which PSC patient is at risk for developing cholangiocellular carcinoma.<o:p></o:p> Alcoholic and non-alcoholic fatty liver and steatohepatitis: Genomic and postgenomic tools have no routine place in the management of these disorders yet. However, as outlined above, mutation analysis of disease modifying genes or postgenomics tools (transcriptomics, proteomics, metabolomics) could also provide important prognostic and therapeutic information. Moreover, this approach could help to answer who does (and does not) get progressive disease with progression from simple steatosis to (N)ASH with fibrosis and ultimately cirrhosis. This could be approached with genetic markers of inflammation and hepatic fibrogenesis and proteonomis/metabolomics, e.g., by identifying markers of oxidative stress and their effects on (serum) proteins (posttranslational modifications) (15).
Certainly, (N)AFL and (N)ASH could become an important area of application for nutrigenomics ("eat and drink right for your genotype"). Recently, the term “alcoholomics” has been
coined to describe the study of genes and proteins that are directly and indirectly affected by alcohol (16). The management of alcoholic liver diseases would also greatly benefit from further identification and quantification of biomakers of alcohol-related liver injury. Direct product of alcohol metabolisms(e.g., acetaldehyde, lipid peroxides) can cause posttranslational protein modifications which can be detected and quantify by proteomics techniques. The observation that alcohol consumption inhibits the incorporation of sialic acid into transferrin and other glycoproteins is already being routinely used as marker of alcohol consumption (carbohydrate deficient transferrin). Proteomics could upscale the qualitative and quantitative analysis of such posttranslational modification to a systematic “holistic” level. Ideally, postgenomics could help to differentiate between ASH and NASH based on postgenomic profiles.<o:p></o:p> <span lang="EN-GB" style="font-family:"Times New Roman","serif";mso-fareast-font-family:"Times New Roman";

mso-ansi-language:EN-GB">3. Future perspectives<o:p></o:p> For monogenetic diseases, multiplex PCR approaches or oliogonucleotide arrays allowing the simultaneous detection of multiple mutations (including disease modifier genes) may be the way to go. There is a need to establish more reliable genotype-phenotype correlations which allow better prediction of clinical course, prognosis and response to (tailored) therapy of monogenetic diseases.
  Similarly, expression profiling by
transcriptomics and proteomics from liver biopsies and their correlation with metabolic and functional consequences (metabolomics) may also help to better predict the clinical course and individualize therapy of complex (oligo- and polygenetic) metabolic liver diseases. However, this information is not yet available since studies obtained such correlations are so far lacking. One way to obtain such information would be the creation of large scale biobanks and databanks containing genetic and expression profiles from diseased human tissues and correlating them with clinical data. Large tissue collections allow getting insight into the great variability of human diseases. The potential use of a biobank, however, requires well standardized tissues, which are associated with detailed medical data. Because of the great number of biological and medical parameters (e.g., type of disease, treatment, genetic polymorphisms, accompanying disease, life style etc.) that influence and characterize the disease of individual patients, hundreds to thousands of samples have to be investigated to cope with biologic/medical diversity. The number of cases analysed even needs to be increased if the approach is not focussed on single genes but aims at elucidating whole regulatory networks in the context of systems biology. Several requirements have to be met, such as international applicable quality standards for sample and data acquisition, validated platforms for sample analysis, information technology solutions supporting sample tracking, data storage, data mining and protecting sample donor privacy.<o:p></o:p>   <span lang="EN-GB" style="font-family:"Times New Roman","serif";
mso-ansi-language:EN-GB">In a pilot project the tissue collection of the Medical University Graz has been developed into a biobank comprising actually

ca. 3 mio. paraffin-embedded normal and
diseased human tissues as well as 30,000 frozen tissues stored in liquid nitrogen. Standard operation procedures for tissue collection and storage were elaborated. Samples are annotated with clinical data concerning diagnosis of disease, follow up as documented by ultrasound, x-ray, CT or NMR, response to therapy, survival, and cause of death. Furthermore an IT-infrastructure has been established comprising data bases to support sample administration and to store detailed sample-associated medical information. Databases were established to administer data generated from tissues by gene expression profiling and tissue microarray analysis. A data mart was designed to enable complex queries combining molecular data with detailed medical information and at the same time protects privacy by preventing re-identification of individual patients. The data mart will be of central relevance for future international data-sharing. Hopefully this approach will allow a better prediction of the clinical course of metabolic and cholestatic liver diseases.<o:p></o:p> <span lang="EN-GB" style="font-family:"Times New Roman","serif";
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mso-ansi-language:EN-GB">Tyers M, Mann M. From genomics to proteomics. Nature 2003; 422: 193-7. <o:p></o:p></pre><pre style="text-align:justify;text-justify:inter-ideograph"><span lang="EN-GB" style="font-size:11.0pt;mso-bidi-font-size:10.0pt;font-family:"Times New Roman","serif";
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<!--[endif]-->Hanash S. Disease proteomics. Nature 2003; 422: 226-32. <o:p></o:p></pre><pre style="text-align:justify;text-justify:inter-ideograph"><o:p> </o:p></pre><pre style="margin-top:0cm;margin-right:36.0pt;margin-bottom:0cm;margin-left:36.0pt;margin-bottom:.0001pt;text-align:justify;text-justify:inter-ideograph;text-indent:-18.0pt;mso-list:l0 level1 lfo2;tab-stops:list 36.0pt left 45.8pt 91.6pt 137.4pt 183.2pt 229.0pt 274.8pt 320.6pt 366.4pt 412.2pt 458.0pt 503.8pt 549.6pt 595.4pt 641.2pt 687.0pt 732.8pt"><!--[if !supportLists]-->4.   <!--[endif]-->Evans WE, Relling MV. Moving towards individualized medicine with pharmacogenomics. Nature 2004; 429: 464-8. <o:p></o:p></pre><pre style="text-align:justify;text-justify:inter-ideograph"><o:p> </o:p></pre><pre style="margin-top:0cm;margin-right:36.0pt;margin-bottom:0cm;margin-left:36.0pt;margin-bottom:.0001pt;text-align:justify;text-justify:inter-ideograph;text-indent:-18.0pt;mso-list:l0 level1 lfo2;tab-stops:list 36.0pt left 45.8pt 91.6pt 137.4pt 183.2pt 229.0pt 274.8pt 320.6pt 366.4pt 412.2pt 458.0pt 503.8pt 549.6pt 595.4pt 641.2pt 687.0pt 732.8pt"><!--[if !supportLists]-->5.

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mso-ansi-language:EN-GB">Evans WE. Pharmacogenomics: marshalling the human genome to individualise drug therapy.Gut 2003; 52 (Suppl 2):10-8. < o : p > < / o : p > < / s p a n > < / p r e > < p r e style="text-align:justify;text-justify:inter-ideograph"><span lang="EN-GB" style="font-size:11.0pt;mso-bidi-font-size:10.0pt;font-family:"Times New Roman","serif";
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mso-ansi-language:EN-GB">Desiere F. Towards a systems biology understanding of human health: Interplay between genotype, environment and nutrition. Biotechnol Annu Rev 2004; 10: 51-84. <o:p></o:p></pre><pre style="text-align:justify;text-justify:inter-ideograph"><span lang="EN-GB" style="font-size:11.0pt;mso-bidi-font-size:10.0pt;font-family:"Times New Roman","serif";
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at an old disease. N Engl J Med 2004; 350: 2383-97. <o:p></o:p></pre><pre
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mso-ansi-language:EN-GB">Perlmutter DH. Alpha-1-antitrypsin deficiency: diagnosis and treatment. Clin Liver Dis 2004;8:839-59.
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mso-ansi-language:EN-GB">Jansen PL, Sturm E. Genetic cholestasis, causes and consequences for hepatobiliary transport. Liver Int 2003;23:315-22. <o:p></o:p></pre><pre style="text-align:justify;text-justify:inter-ideograph"><span lang="EN-GB" style="font-size:11.0pt;mso-bidi-font-size:10.0pt;font-family:"Times New Roman","serif";
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mso-ansi-language:EN-GB">Jansen PL. Hepatology in the 21st century. Gene transfer, hepatocyte transplantation, DNA chips, cyberspace and ... a friendly hospital. Neth J Med 1999;55:287-92. <o:p></o:p></pre><pre style="text-align:justify;text-justify:inter-ideograph"><span lang="EN-GB" style="font-size:11.0pt;mso-bidi-font-size:10.0pt;font-family:"Times New Roman","serif";
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mso-ansi-language:EN-GB">Day CP. The potential role of genes in nonalcoholic fatty liver disease. Clin Liver Dis 2004; 8: 673-91. <o:p></o:p></pre><pre style="text-align:justify;text-justify:inter-ideograph"><span lang="EN-GB" style="font-size:11.0pt;mso-bidi-font-size:10.0pt;font-family:"Times New Roman","serif";
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