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Roadmap to DILI research in Europe. A proposal from COST action ProEuroDILINet

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ABSTRACT

In the current article the aims for a constructive way forward in Drug-Induced Liver Injury (DILI) are to highlight the most important priorities in research and clinical science, therefore supporting a more informed, focused, and better funded future for European DILI research. This Roadmap aims to identify key challenges, define a shared vision across all stakeholders for the opportunities to overcome these challenges and propose a high-quality research program to achieve progress on the prediction, prevention, diagnosis and management of this condition and impact on healthcare practice in the field of DILI. This will involve 1. Creation of a database encompassing optimised case report form for prospectively identified DILI cases with well-characterised controls with competing diagnoses, biological samples, and imaging data; 2. Establishing of preclinical models to improve the assessment and prediction of hepatotoxicity in humans to guide future drug safety testing; 3. Emphasis on implementation science and 4. Enhanced collaboration between drug-developers, clinicians and regulatory

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Atypical DILI phenotypes
Integrative multi-scale data
Networking
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scientists. This proposed operational framework will advance DILI research and may bring together basic, applied, translational and clinical research in DILI.

1. Introduction

The vast majority of adverse clinical hepatic reactions to drugs are *idiosyncratic* which occur at therapeutic doses. *Idiosyncratic* drug-induced liver injury (DILI) is an unexpected, multifaceted, host-dependent, and potentially serious adverse reaction to the use of conventional medicines, herbal products, or dietary supplements (HDS). This occurs in only a small proportion of exposed individuals, jeopardizes patient safety and represents one of the most difficult liver disorders to predict, diagnose and treat [1]. Globally, 1 to 1.5 million people suffer from the clinical consequences of hepatotoxicity each year, based on extrapolation of data from a population-based study from Iceland [2]. It is estimated that drugs are responsible for 2–5% of hospitalisations for jaundice [3], 10% of cases of hepatitis in adults, and 13–17% of cases of fulminant hepatitis [4,5]. In 23% of cases of clinically overt hepatotoxicity, hospitalisation is required and in about 8–10% of cases, elevated liver enzymes do not resolve after withdrawal of the offending drug. The pharmacological groups most frequently involved in DILI in Western countries are antimicrobials, antineoplastic/ immunomodulatory agents, cardiovascular and musculoskeletal and anti-inflammatory drugs; while herbal compounds and dietary supplements including those containing androgenic anabolic agents are responsible for an increasing number of cases of hepatotoxicity [6,7].

The absence of a consistent drug signature with a wide range of presentation of DILI and the lack of specific biomarkers challenge the diagnosis of this entity. The complexity of underlying mechanisms coupled with species differences in drug biotransformation and immune responses has hampered efforts to develop reproducible animal models of DILI. Therefore, conventional preclinical toxicological testing has limited translational potential in predicting adverse hepatic reactions in humans [8].

Undoubtedly, adverse liver reactions and their monitoring place a burden on patients and health services. Attrition of the drugs during the development and their withdrawal post-marketing raises the cost of drug development. Patient safety during clinical trials and in clinical practice are an important challenge for clinicians, the pharmaceutical industry, and regulatory agencies worldwide.

The Prospective European Drug-Induced Liver Injury Network Cost Action 17–112 (www.proeurodilinet.eu), comprising 27 European countries, was initiated in 2018 to highlight and start to address these multi-faceted challenges. This consortium has addressed both state-of-the-art advances in preclinical human-relevant models and clinical DILI [1,9–11], and in collaboration with international organizations provided a blueprint for clinical and pharmacovigilance practice guidelines [12,13]. Through a series of systematic reviews [14–17] this network has identified translational gaps as well as areas where high-quality evidence is lacking. Furthermore, an International Consensus Conference on Drug-Induced Autoimmune-like Hepatitis was jointly held with the International Autoimmune Hepatitis Group to agree on terminology, harmonization of criteria, diagnosis, and management of this important clinical issue [18]. Similarly, collaboration with liver patient groups has been established to highlight the importance of the patient perspective on DILI, paving the way for an information day on DILI to explain in layman's terms what DILI is.

In parallel, ProEuroDILINet has secured partnership with an ongoing, major European IMI scientific project TransBioLine (Translational Safety Biomarker Pipeline). This important initiative was conceived to overcome well-recognized and substantial gaps [19] in biomarker discovery. This partnership is addressing the development, validation, regulatory qualification, and application of safety biomarkers, with the goal of generating a fundamental change in the way hepatic drug safety is assessed in clinical trials and how toxicity is diagnosed and managed in clinical practice. Promising first steps of the collaboration have led to the identification of candidate serum protein biomarkers of DILI in humans through tandem mass tag-based quantitative proteomic profiling [20].

We propose a DILI roadmap that aims to highlight the most important priorities for research in preclinical and clinical safety science. The roadmap will be developed and set out along four strategic lines:

2. Creation of database and optimised case report form for prospective identification of DILI cases and well-characterised controls, biological samples, and imaging data

2.1. Creation of a prospective and integrative database of DILI patients: the ID-DILI

Currently, prospective registries are the most valuable source of data for *idiosyncratic* DILI research. These provide high-quality information from a large number of deeply phenotyped patients enrolled using a standardized protocol [6,21–23]. However, very few have controls with an established alternative diagnosis prospectively enrolled and evaluated with similar rigour [24]. In addition, comparability between registries is to some extent limited due to differences in data collection, case definition, or causality assessment [6,25]. Thus, in the context of a relatively low incident condition such as DILI, the creation of a prospective and integrative database has great interest.

To do so, the first step is to map the databases related to *idiosyncratic* acute DILI to enable interoperability, data integration and homogenization from several different databases, which would allow for more comprehensive analyses.

However, information in these resources may lack standard criteria, such as metadata.

Once this list of metadata is detailed, information from mapped databases could be collected and integrated in the proposed prospective database. Information to be included may comprise standard prospective registry information (demographics, clinical data), linked omics-related data, and highly informative digital imaging tests from DILI patients. This database will lead to an operational framework to foster DILI research and may drive a paradigm shift towards a holistic approach to the disease.

2.2. Challenges in the establishment of causality assessment

While awaiting the development of specific biomarkers for DILI the diagnosis relies on the establishment of a temporal relationship and the exclusion of alternative liver disorders. The current liver-specific RUCAM/CIOMS scoring system to aid in the diagnosis of DILI,

developed more than 30 years ago, was never evidence-based and suffered from poor inter-rater reliability [26]. Using data from two large prospective DILI registries, a revised electronic version, RECAM (http://dilirecam.com/), was developed as a more objective, user-friendly, reliable and validated scoring system [27]. However, it is not designed for cases with more than a single suspect drug or for HDS cases, and further refinements with long half-life agents such as monoclonal antibodies or in cases of drug-induced autoimmune-like hepatitis and validation in other cohorts are needed to answer open questions such as whether it should replace RUCAM scoring or whether the expert opinion model is still the plan for the future in clinical drug development.

2.3. Prospective identification and characterization of atypical DILI phenotypes

The creation of the ID-DILI will foster the prospective identification and characterization of specific and atypical DILI phenotypes, a topic of great importance to create new knowledge in DILI research. Immune checkpoint (ICP) inhibitors have changed the paradigm in oncology, resulting in improved survival in patients with advanced cancer, but at the expense of immune-mediated adverse events, including a new phenotype of DILI [28,29]. In addition, another emerging clinical phenotype is drug-induced autoimmune-like hepatitis (DI-ALH) [18]. The available evidence on DI-ALH consists exclusively of retrospective analysis of prospective DILI cohorts [30–32]. Notably, in addition to conventional medications, SARS CoV-2 vaccines have been identified leading to a DI-ALH phenotype [33]. Nonetheless, despite sustained efforts in describing the clinical characteristics of this atypical DILI phenotype, there is still a lack of information derived from biological samples from these patients. Such information would be helpful in the discovery of prognostic biomarkers that predict the need for immunosuppression in these patients. Study of the mechanisms of immune related liver injury with ICP inhibitors, acute hepatitis after SARS-CoV2 vaccination and DI-ALH will improve our understanding of the underlying pathways in diseases which diagnosis relies on the exclusion of other liver disorders and have a genetic background. Further investigations focused on DI-ALH might shed light on both “idiopathic” autoimmune hepatitis (AIH) and DILI. Biologic DILI (BILI) is a very important new area, especially with the explosion of monoclonal antibodies to treat many diseases and the occurrence of BILI independent of the generation of haptenizing metabolites. This problem needs to be better understood and mitigated.

In addition, DILI in children is under-researched. Paediatric acute liver failure is a serious and sometimes life-threatening entity, requiring liver transplantation, in which drugs are one of the main known etiologies [34,35]. Recent progress in the understanding of genetics and particularly pharmacogenomics makes it possible to perform further studies in children who experience hepatotoxicity [36]. Indeed, pharmacogenomic testing for particular genes has been shown to be of value in children with epilepsy who need treatment with lamotrigine [37]. However, studies focused on DILI in the paediatric population are still scarce [38], and treatment of the condition in this population is merely extrapolated from adults [17]. Therefore, the existing gap in knowledge about DILI in this vulnerable population requires urgent attention.

DILI due to HDS represents a growing concern due to the increasing proportion of HDS- related cases in registries [39,40]. An increasing proportion of patients with drug-induced acute liver failure have HDS as the etiology [41], and Asians appear to be at increased risk of developing HDS-induced acute liver failure, although the mechanisms underlying ethnicity as a risk factor remain to be investigated [42,43]. Nonetheless, much progress has occurred in the understanding of the pathophysiology of liver injury associated with HDS. For instance, Polygonum Multiforum and green tea extract is among the most well-documented HDS leading to predominantly hepatocellular liver injury, with a very well-defined biochemical phenotype and strong genetic HLA association [44–46]. Furthermore, new agents such as *Tinospora Cordifola*, turmeric and Kratom have recently been identified as causes of liver injury [47]. The use of these nonprescription and accessible products that can be directly purchased online, calls for urgent action.

Finally, chronic DILI following acute DILI ranges from 3.4% to 39%, 6 to 12 months after discontinuation of the offending agent [48]. Variability may depend on the criteria used and the characteristics of the patient because there is usually little information about confounding factors such as preexisting steatotic liver disease [49]. Aside from vanishing bile duct syndrome, whose unfavorable prognosis is well-established [50], more research is needed into long-term adverse outcomes of chronic DILI patients.

In this sense, the ID-DILI will aid in characterizing the clinical presentation of liver damage caused by conventional medications and HDS, while the collection of biological samples will both increase knowledge of the underlying hepatic mechanisms of these products in the liver – and increase opportunities for biomarker discovery.

2.4. Development of an adaptive and optimized case report form to capture real-world information in DILI patients

DILI is a complex condition in which both host and drug factors interplay and contribute to the susceptibility and presentation of liver damage [51]. Although the existing prospective registries include a substantial amount of valuable information for the study of DILI, there is a need to explore new tools that collect further information to provide a more holistic picture of the condition.

In this regard, the exposome provides a better understanding of the cumulative effects of environmental exposures and biological responses from conception onwards [52]. Currently, recent advances show that evidence of exposome-wide association studies in liver diseases are scarce and limited to conditions other than DILI [53]. For future research into complex liver diseases, the exposome provides novel, additional insights into innovative study designs to test novel mechanistic hypotheses in DILI. Exposome features can be measured in two ways - either through: i) A *bottom-up* approach, i.e., focusing on each category of external exposure that would be summed up to estimate individual exposomes; or ii) A *top-down* approach, that uses untargeted omics methods to measure features of the exposome in biological fluids [54]. Thus, the decision on which approach is more appropriate will depend on the study hypothesis. For instance, the top-down strategy may help in discovering new mechanistic pathological pathways of the disease, whilst the bottom-up perspective is appealing when conducting an analysis of external determinants of the condition and planning intervention and prevention actions [55]. Although there are no studies addressing the study of the exposome in DILI, exposome-wide association studies in other liver diseases have been recently published. To detect environmental chemicals and endogenous metabolites in patients with primary biliary cholangitis and primary sclerosing cholangitis, Walker et al. developed both individual and integrated exposomic- and metabolomic-wide association analyses [53]. Therefore, the study of the exposome in DILI will require a new optimized and standardized data questionnaire that needs to be extensive, to capture all endogenous and exogenous exposures of interest, and adaptive, i.e., to allow its use in a broad array of studies and populations, along with the serial recollection of biological samples that may allow to test novel and complex mechanistic hypotheses.

Importantly, new case report forms should include patient liver histology data for prospective registries. The importance of liver biopsy in the differential diagnosis of DILI has been reported in previous studies. Suzuki *et al.* studied DILI and AIH biopsies where histological findings may overlap [56]. Indeed, prominent intra-acinar lymphocyte infiltrate and canalicular cholestasis, without the presence of AIH features (portal inflammation, rosettes, plasma infiltrates), suggests DILI. More recently, in a re-assessment of 50 cases included in the DILIN study, liver histology information was deemed helpful in confirming the diagnosis of DILI [57]. Currently, the information obtained from liver

biopsies is a redacted clinical narrative, which makes analysis difficult due to the different terminology used by different pathologists. Thus, evolving case report forms should include digitized liver histology/biopsies along with the development of text-processing machine learning models to extract structured information from narrative descriptions to promote the use of highly informative histological information for future DILI research. Ideally, centralized reading of biopsies by an experienced pathologist in DILI should be included in prospective cohort studies.

3. Preclinical models in DILI to improve the assessment and prediction of hepatotoxicity to guide future drug safety testing

As a major cause of acute liver failure and attrition of drug development, it is crucial to elucidate the mechanisms and idiosyncrasy of DILI. To this end we propose a multidisciplinary approach using patient-derived preclinical models with real-time, non-invasive imaging and integrative multi-omics analyses, complemented with conceptual frameworks (Adverse Outcome Pathway, AOP), liver-chip and other emerging ^{3}D–^{4}D multicellular in vitro platforms and humanized animal models to delineate mechanisms of relevance to human DILI. The emerging role of hepatic extracellular vesicles (EVs) in DILI positions them as a promising preclinical tool for the exploration of novel biomarkers and potential therapeutic agents (Fig. 1).

3.1. Advanced in vitro approaches to move forward personalized medicine in DILI

3.1.1. Patient-derived pluripotent stem cells

Despite their popularity as in vitro models in DILI research, hepatocyte-derived carcinoma cell lines do not faithfully reproduce primary hepatocyte metabolic functions and hence their use blur the findings of relevance for human DILI research. In addition, although primary human hepatocytes (PHH) are highly relevant for human DILI research, culture of PHH has shortcomings that preclude their routine use for drug screening, most importantly the short-time maintenance of maturation phenotype leading to low expression of cytochrome P450s during culture, which limits and misrepresents drug metabolism [58].

Human induced Pluripotent stem cells (iPSCs) have been increasingly used to generate human in vitro systems, for experiments evaluating human liver physiology and pathobiology. They have extensive proliferation, genetic stability, and the capacity to differentiate to different liver cell types [59]. iPSCs show great potential for personalized medicine and to evaluate individual response to drugs as they can be generated from patients with DILI or from patients' populations presenting specific susceptibility. Moreover, genomic traits can be easily introduced given the flexibility to genetically manipulate them. Polygenic architecture reflected by hepatocyte like cells derived from iPSCs have been shown to be important to recapitulate multiple pathways implicated in hepatoxicity [60,61]. Genetic modification of patient-derived PSCs further represents a major advantage of this system to model DILI [62]. On the other hand, a multicellular system with the same genetic background would offer the possibility to link the toxic response to the other pathogenic mechanisms of the disease [63]. In this regard, iPSC-derived multicellular liver organoids have shown good predictive value as a platform for DILI risk assessment [64,65]. Thus, differentiation of iPSCs into hepatocyte-like cells [63,66], as well as non-parenchymal cells (NPCs) [67–69] such as tissue-resident macrophages [70] and hepatic stellate cells [71] has been an intense area of research to improve the maturation of hepatocyte-like cells and their use to predict drug hepatotoxicity and human DILI.

3.1.2. Complex cell culture configurations

Despite their low cost and easy to use, two-dimensional (2D) cultures

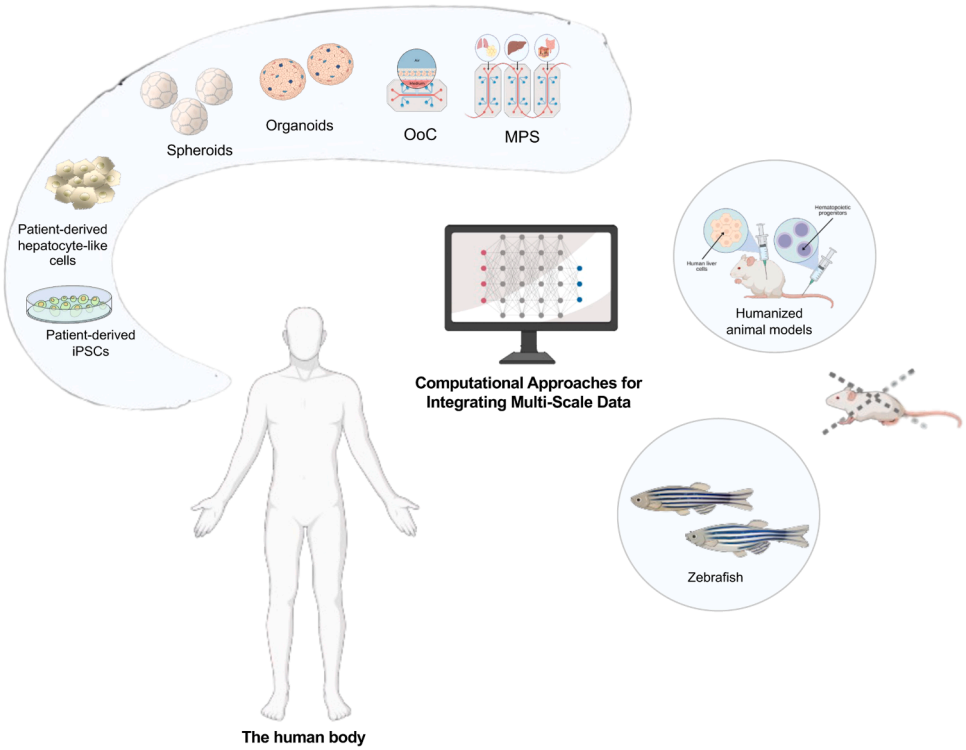

Fig. 1. Potential future steps in preclinical DILI research. The interplay of host- and drug-specific factors in DILI makes the use of patient-derived cells and complex in vitro cell models a critical need. Among in vivo model approaches, humanised mouse models are the most promising, although the EU is taking tangible steps towards the future goal of complete replacement of all animals used for scientific purposes. Finally, the future strategy for DILI research should include computational approaches to integrate data generated by both in vitro and in vivo assays in combination with genetic, epigenetic, and clinical information obtained from DILI patients.

do not mimic the cellular microenvironment and complex architecture of in vivo *models*. This shortcoming limits the predictive power and potential of these in vitro models for assessing the toxicity of xenobiotics [72].

Novel 3D models are presented as alternative systems due to their ability to replicate both biological and mechanical cues of the native liver niche, namely cell-to cell, cell-to-ECM, oxygen/nutrients/paracrine gradients and biological fluxes [73–76]. 3D systems include spheroid cultures, organoids, bioprinting (3D and 4D), microphysiological (MPS) and organ-on-a-chip (OoC) systems. These systems vary in their complexity and monitoring, allow control of the flow of fluids and nutrients, gradients of compounds and gas exchange, and can also be adapted for high-throughput screening (HTS) and a larger scale of production [73–77].

Spheroids are based on the cells' ability to self-aggregate into spheroids, while liver organoids correspond to self-organizing, organ-specific multicellular structures that mimic the structure and function of the human liver when cultured under specific media and matrix conditions [74]. Recently, co-differentiation strategies in 3D culture systems have been described to obtain functional hepatic organoids [78], which have been already used to test the hepatotoxicity of currently available drugs in the clinic [79].

The 3D printing technology constitutes a novel fabrication technique that resorts to bioinks (cell-laden biomaterials) and involves layer-by-layer deposition of cell-embedded polymers guided by a computer-aided design (CAD) software, for the creation of complex structures on-demand. The 4D bioprinting adds to the 3D printing the use of smart materials able to reshape themselves in response to different stimuli, e.g., temperature, pH, and light, to closely mimic the dynamic responses of tissues in vivo [80]. Thus, 4D bioprinting technology is expected to enable the production of bioprinted human liver tissues containing both human liver cells and immunocompetent cells within a defined architecture, with the aim of detecting DILI during the non-clinical phase.

Finally, OoC and MPS have the advantage to integrate different human cell lines while incorporating complex structures, such as vasculature and barrier function, thereby replicating the organ's architecture more closely. Moreover, the integration of impedance sensing in OoC models could provide a real-time non-invasive means to monitor critical barrier functions, such as the endothelial barrier in liver models. This would allow for continuous evaluation of organ-level response to drug exposure and capture the impact of DILI progression on other organs in the context of interconnected OoC models, e.g., liver-kidney-gut model. These complex in vitro models could improve the success of drug candidate translation into the clinic as well as non-clinical safety testing. This opens up new opportunities for the pharmaceutical industry to incorporate microphysiological systems, including organ-on-chip model technologies, into drug development to predict drug-induced liver injury.

In terms of imaging, advanced in vitro models lend themselves well to longitudinal live imaging and progress is made towards their compatibility with high-content screening (HCS), enabling researchers to track dynamic cellular and subcellular events over time. The integration of novel imaging techniques could capture cellular (multiphoton), intracellular (lipid imaging with quantitative phase tomography) and mechanical changes (Brillouin microscopy, optical coherence elastography) in response to DILI progression.

3.2. Humanized mouse models: a game-changer in DILI research

While useful for first-step strategies such as large drug screening platforms, in vitro approaches lack the integrative complexity of in vivo models. To circumvent this shortage, humanized mouse models have been developed to increase the relevance of the findings of DILI research to the clinical arena [10]; while ongoing improvements in genetic engineering and cellular reprogramming technologies will likely enhance the fidelity of these models in the years to come expanding greatly their utility for DILI research.

Several mouse lines with humanized liver have been generated to date, all of which require an immunosuppressive environment in order to allow for efficient engraftment of the xenotransplanted human hepatocytes, which gradually are expected to repopulate the murine liver as the endogenous mouse hepatocytes die. Among these models, the FRGN mice model, a triple ($Il2rg^{-/-}$/$Rag2^{-/-}$/$Fah^{-/-}$) knockout line in the NOD background, has several advantages compared to other humanized models, e.g. TK-NOG, or uPA/SCID, including the possibility to generate double chimeras with humanized adult hepatocytes and hematopoietic cells [81], as well as the deletion of mouse NADPH-cytochrome P450 oxidoreductase gene (POR) to unmask the metabolism of drugs through the activities of human CYPs. In this regard, the parallel xenotransplantation of human hepatocytes and human stem CD34 + cells would allow the reconstruction of a murine liver endowed with both human hepatocytes and hematopoietic cells, whose interplay mimics a scenario of greater relevance for the human disease".

In addition, humanized mice can be genetically modified to study specific pathways. For example, the overexpression of STARD1, illustrates the potential of this model to study acetaminophen and alcohol hepatotoxicity with features similar to human subjects, including zonal-dependent injury coinciding with the predominant expression of StARD1 in perivenous zone [82,83]. Recent findings reported the improvement of humanized models with the repopulation of mouse liver with human hepatocytes and NPCs, including human immune, endothelial and stellate cells. The implementation of this model should be useful for studying signaling pathways involved in DILI and its modulation by NPCs [84].

3.3. Mode of liver injury and impact of metabolic liver disease on DILI

An important limitation towards improving the prediction, and diagnosis of DILI is to understand the mode of liver injury by drug exposure. Liver damage in response to drugs reflect mainly a hepatocellular or cholestatic injury, which exhibit different biochemical and morphological characteristics underlying distinct modes of cell death [85]. Thus, understanding the mode of cell death in DILI is a key step for the identification of putative targets of intervention. While discrimination of the type of cell death in DILI may be drug-specific, drug-induced cell damage involves multiple pathways relying on intracellular compartments, particularly endoplasmic reticulum (ER) and mitochondria, whose cross-talk determines whether and how cell death ensues. Hence, discerning whether chronic ER stress through different signaling pathways (e.g. IRE1, PERK and ATF6), and/or mitochondrial-dependent oxidative stress via hyperactivation of stress kinases (e.g. JNK) by an amplification loop involving JNK1/2 and SAB mediates drug-induced cell death and liver injury may be crucial to identify potential targets for the treatment of DILI [86–88].

In addition to liver injury, drugs can also disrupt metabolic pathways leading to drug-induced fatty liver disease (DIFLD), a condition of particular concern in the elderly due to the polypharmacy of this population. Not only drugs can elicit DIFLD but existing metabolic alterations, such as metabolic-associated steatotic liver disease (MASLD), the most common cause of chronic liver disease associated with obesity and type 2 diabetes, can disrupt hepatic drug metabolism and/or sensitize to liver injury. Higher risk of DILI in obesity is related not only to increased activity of several cytochromes P450, such as CYP2E1, which is accountable for the generation of toxic intermediates like NAPQI in the case of APAP, but also, MASLD-mediated disruption of mitochondrial function and impairment of antioxidant defense can contribute to the sensitization of drugs like APAP in obese individuals. As the type rather than the amount of fat is a critical determinant of progression of MASLD towards advanced stages [89], appropriate models of diet-induced steatosis may be useful to elucidate the contribution of specific lipid species in DILI susceptibility. This premise has been best illustrated in the role of cholesterol accumulation, particularly in mitochondria, in

APAP sensitization and a combination of the above mentioned models including human-based liver on-a-chip, precision-cut liver slices and 3D cell structures exposed to lipid loaded conditions (e.g. fatty acids, carbohydrates, glucose-derived metabolites, cholesterol) may be useful to screen the impact of steatosis into the pattern of drug metabolizing enzyme and drug hepatotoxicity, findings that should be validated in in vivo models of MASLD [90–96].

3.4. Zebrafish model: simplicity to get effectiveness

Among the simplest in vivo models, zebrafish (*Danio rerio*) offers an effective and cost-efficient alternative for DILI studies [97]. With their transparent embryos, zebrafish allow direct visualization of internal structures and processes, facilitating the study of drug effects on liver morphology and function. Conservation of liver functions as well as major enzymes makes zebrafish larvae an advantageous model for studying drug metabolism and liver injury [98].

In the context of HCS, zebrafish are particularly attractive due to their high fecundity, small size, compatibility with microtiter plates and automated imaging via the ease of direct immersion in media containing drugs. These, together with the availability of a multitude of mutant, CRISPR and/or transgenic strains for zebrafish genes that exhibit conserved functional similarities with their corresponding mammalian orthologs, make this species a high-potential tool for large-scale DILI studies [97].

However, there is still a need for identifying common and divergent mechanisms between zebrafish and humans, which shall be done via comparative studies. Transgenic lines that will report expression of DILI biomarker genes can be developed to conduct screens for DILI response in a simple preclinical setting. In addition, zebrafish xenograft models, enabling transplantation and survival of human cancer cells including those of the liver in vivo, have already gained popularity to test differential effects of drugs, genotypes, as well as microenvironments [99]. Xenografts of patient-derived hepatocyte-like cells into zebrafish larvae for drug screening can further help translate the preclinical model repertoire of DILI to the clinic.

3.5. Computational approaches for integrating multi-scale data in DILI research

In silico models have reduced the cost of DILI risk assessment due to their ability to screen a large number of chemical compounds in a short time, even before they are isolated or synthesized [100]. In a further step, mechanism-driven modelling, such as the AOP, has substantially advanced the field of chemical hepatotoxicity [101,102] by allowing a multi-scale data integration of different non-animal tests.

However, due to the sheer amount of data currently generated in omics-based clinical and in vitro studies (genomics, transcriptomics, proteomics, metabolomics), more effective and powerful data-analysis tools are needed. Machine learning and artificial intelligence are increasingly being applied in system biology approaches for fundamental understanding of cellular network dynamics [103] and their application for data integration and analyses in DILI research [104].

Moreover, DILIsym, a quantitative systems pharmacology (QST) model of drug-induced liver injury, is one of the few in silico models that combines statistical approaches with clinical data from patients and mechanistic in vitro systems designed to test bile acid transporter inhibition, mitochondrial dysfunction and oxidative stress. DILIsym is a platform created as part of the DILIsym Initiative, a public-private partnership involving scientists from industry, academia and the Food and Drug Administration (FDA), to predict idiosyncratic DILI events in humans. The software simulates the mechanistic interactions and events from drug administration through the progression of liver injury and regeneration [105]. DILIsym has already been used to model idiosyncratic DILI events associated with troglitazone [106], tolvaptan [107] and cannabidiol and valproate [108]. Both metabolic adaptation and immune tolerance are likely to be important contributors to the susceptibility and/or severity of DILI, but are not well demonstrated. Incorporating these mechanisms into DILI models seems challenging and needs to be understood.

These advanced computational approaches will facilitate the identification of key characteristics in the different pleiotropic forms of DILI, which will assist in the development of improved in vitro models for DILI risk prediction [65] and the identification of efficacious biomarkers [10].

3.6. Perspectives of extracellular vesicles (EVs) in DILI

Both in vivo and in vitro investigations provide evidence supporting the notion that hepatocyte-derived EVs are significantly influenced by drug metabolism, altering composition, morphology, and abundance of their protein cargo [109]. Hepatotoxic drugs can affect the incorporation of liver-specific mRNA (e.g., *ALB* gene) [110], miRNA (e.g., miR-122) [111], and proteins (e.g., CPS1, MAT1, COMT) into the EVs released by hepatocytes [112,113], and perhaps event alterations of the lipid composition of the membrane bilayer. Notably, EVs have been found to carry proteins covalently modified with amoxicillin, flucloxacillin, and nitroso-sulfamethoxazole, among others. Subsequently, these EVs can be captured by monocytes, and it has been demonstrated that they possess the capability to activate naïve T cells from human donors [114]. This is relevant as evidence suggests that most idiosyncratic DILI cases are mediated by the adaptive immune system [115,116]. However, the definitive triggering stimulus responsible for these cases remains unidentified. EVs are hypothesized to fulfil a significant role, not only as antigen presenters but also as carriers of reactive metabolites capable of inducing oxidative stress [117,118] or activate cytochromes [119]. Besides their potential contribution to the onset of DILI, released EVs in plasma may serve as putative biomarkers for idiosyncratic DILI.

Nanotechnological interventions have emerged in the last few years as promising approaches for the prevention and treatment of different diseases. Indeed, nanoparticles possess a range of characteristics that would make them particularly intriguing for the treatment of DILI in the near future such as their propensity to accumulate in the liver, ability to pass through the fenestrations of the liver sinusoid and their high loading capacity and biocompatibility [120].

4. Clinical research and healthcare system implementation

4.1. DILI as a rare disease and possibility of family studies

The European definition of a rare disease, as defined by the European Union Regulation on Orphan Medicinal Products from 1999, is a disease that affects no more than 1 person in 2000 in the European population. Since exposure to a specific drug causing DILI is needed to trigger the disease, this requirement is met for some forms of DILI only since estimates for frequency of a specific form of DILI range from 1 in 20 for

Table 1
Incidence of selected forms of DILI.

Causative Drug	Frequency in those exposed to drug	Reference
Amoxicillin-clavulanate	1 in 2350	[2]
Amoxicillin-clavulanate	1 in 641	[123]
Azathioprine	1 in 133	[2]
Diclofenac	1 in 9148	[2]
Flucloxacillin	1 in 7065	[124]
Isoniazid	1 in 19	[121]
Isoniazid	1 in 71	[2]
Infliximab	1 in 148	[2]
Nitrofurantoin	1 in 1369	[2]

Data are from predominantly European and Chinese studies but frequencies may differ for other ethnicities.

those prescribed isoniazid to 1 in 9148 for diclofenac (Table 1) [2,121]. While DILI may have been considered to be a rare disease based on population estimates, including 13.9 cases per 100,000 people in France [122], the fact that drug exposure is a crucial step in disease development is important, with recent detailed population studies facilitating a better understanding of disease frequency [2,123,124]. In addition, the various published epidemiological surveys on DILI all suggest that the data reported is likely to be an underestimate of true frequency [2,121,122].

Some forms of drug-induced toxicities are listed by the rare disease inventory, ORPHANET (https://www.orpha.net/consor/cgi-bin/index.php), including drug-induced autoimmune hemolytic anemia, drug-induced localized lipodystrophy, drug-induced lupus erythematosus and drug-induced vasculitis but, importantly, DILI is not listed. This is probably because the incidence is higher than the formal definition of a rare disease when exposure data based on particular drugs is considered. However, it is also clear that DILI does not meet the normal requirements for being a common disease but that the approaches used to study rare diseases may also be applied to DILI, especially for drug-specific DILI and DI-ALH, to improve our knowledge and understanding.

While nearly all genetic diseases are rare diseases, not all rare diseases are genetic diseases, with environmental factors often making a crucial additional contribution. Rare diseases are not always due to a single gene (monogenic) and may involve several different genetic risk factors. In terms of frequency, DILI may best fall into a "grey area" that is neither a rare disease nor common disease. It also meets the definition for being a complex or multifactorial disease. This contrasts with “simple” genetic diseases that are caused more directly by mutations in a single gene. The data collected to date on genetic risk factors for DILI seem most consistent with it being a complex disease, but with relatively fewer risk alleles compared with typical complex polygenic diseases which usually involve a large number of risk alleles, often with a small contribution to risk from each. Examples of such diseases include type II diabetes, coronary heart disease and a range of common cancers.

DILI has several characteristics of a monogenic disease, especially the forms observed with certain commonly prescribed causative drugs. DILI due to flucloxacillin has a strong genetic predisposition; 85% of patients with DILI carry HLA-B* 57:01 while its population prevalence is about 5% [125,126]. Therefore, family studies as an alternative to case-control studies involving unrelated individuals might be a useful means of obtaining new insights into genetic risk factors. It is extremely challenging to perform such studies on DILI because of the need for more than one family member to be exposed to the causative agent. However, since certain drugs causing DILI are very widely prescribed, it seems likely that several members of families will, or have been exposed to these drugs over their lifetime. There are a few studies in the literature consistent with familial clustering in relation to several different drug causes of DILI. The oldest of these concerned phenytoin hepatotoxicity and involved studies on toxic metabolites in lymphocytes [127]. Lymphocytes from patients with phenytoin DILI showed dose-dependent toxicity as did cells from parents and a sibling of some patients. A further study using a similar approach followed up another large family where three siblings had suffered hepatitis and other adverse drug reactions following phenytoin prescription [128]. Again, lymphocytes from some but not all siblings naive to phenytoin showed similar toxicity to the drug-exposed individuals. A broadly similar approach was taken independently in studies on another hepatotoxic drug amineptine [129]. This approach could be readopted with the inclusion of updated in vitro methods for the study of DILI including use of T-cells and has the advantage that drug exposure in other family members is not required as responses in vitro can often be detected in T-cells from unexposed individuals [130]. The studies summarized above did not involve any genetic analyses, but this reflects the fact that they were performed prior to the 1990s.

Two additional case reports involving DILI in families are more recent and provide accounts of siblings showing DILI after amoxicillin and mercaptopurine treatment, respectively [131,132]. These are purely descriptive reports and did not involve any in vitro or genetic analyses but are useful in confirming susceptibility within families.

As a way forward, genome sequencing studies on families with more than one affected member could be helpful in confirming data collected from case-control studies and in establishing the contribution to DILI susceptibility from rare genetic variants not detected in population studies.

4.2. *DILI risk stratification and prognostic biomarkers including pharmacogenetic studies*

As reviewed recently, international case-control studies have already provided important insights into genetic risk factors for DILI [133]. Until genome-wide association studies (GWAS) were applied to risk, the major contribution of HLA genotype to DILI susceptibility was underappreciated. GWAS on other diseases typically uses large numbers of cases and controls but in general most progress on identifying genetic risk factors for DILI to date has involved hundreds of cases; not the thousands that are generally included in GWAS. While there has been some success, particularly in relation to finding HLA associations, there is also evidence that other genetic risk factors are involved albeit with a smaller contribution and therefore more difficult to detect without studying large numbers of cases [61]. There is also still uncertainty on whether these additional risk factors are drug-specific, or for DILI generally. While one study has suggested that different DILI phenotypes may have common genetic risk factors regardless of causative drug, this has not yet been confirmed independently and the data used to make this conclusion was obtained from a relatively small population [61]. Ideally, we need larger studies on DILI generally and on specific drug causes of DILI. The largest GWAS published to date on DILI generally includes just over 2000 cases [134]. Larger studies may well identify additional risk factors, depending on the extent of their individual contributions, which could be helpful in developing approaches for risk stratification such as polygenic risk scores. Up to the present, we have two different published polygenic risk scores for DILI [61]. Both suffer from specific limitations that need further investigation; in one case, the score seems to be one that is general for certain DILI phenotypes independent of causative drug but is very complex involving approximately 25,000 different variants [61], whereas the second is simple but applies only to one cause of DILI, amoxicillin-clavulanate [135]. Further studies are needed to confirm and further develop these findings.

A systematic review has highlighted the need for biomarkers that distinguish DILI from acute liver injury related to alternative etiology, as well as those with a potential to identify serious adverse outcomes from acute DILI [19].

Biomarkers are urgently required for DILI detection during drug development, monitoring during clinical trials, early diagnosis in clinical practice and stratification of individuals whose disease will progress to acute liver failure or chronic liver disease. MicroRNAs (miRNAs) are small non-coding RNA molecules with promising properties as candidate circulatory biomarkers. They remain remarkably stable in biofluids, including plasma, and their circulatory profile can often be linked to tissue-specific expression [136]. The traditional biomarkers for DILI are similar to those used for diagnosis of other liver diseases, i.e., transaminases, alkaline phosphatase and bilirubin. Since these can be measured quickly and accurately in a clinical situation, they offer certain advantages over other biomarkers. A recent study evaluated a range of candidate DILI biomarkers in serum or plasma samples from both DILI cases and controls [137]. The biomarkers investigated were mainly proteins, but the microRNA miR-122 was also included. Glutamate dehydrogenase was found to be a useful biomarker for DILI identification but for prediction of progression to acute liver failure, keratin-18, osteopontin and macrophage colony stimulating factor receptor appeared most promising. A limitation of this study is that only approximately 250 DILI cases were studied with not all assays

performed on all samples, detailed follow-up on outcomes was not always available and there was considerable heterogeneity in DILI phenotypes and causative drugs. To overcome these limitations, a larger study on biomarker identification and qualification for DILI (TransBioLine) is currently in progress [24]. Finally, the effect of underlying disease (e.g. cancer, cardiopulmonary disease, etc. as well implicated drugs on the "fitness" of liver and underlying metabolic or pharmacologic stress (to mitochondria, ER, etc.) and their contribution to both mild or severe liver injury needs more understanding with respect to biomarkers and pathogenesis.

4.3. Artificial intelligence-based integrative research

Artificial intelligence can be defined as mathematical computer-based processes to design algorithms to support human decisions. Notably, the use of AI strategies to develop diagnostic/prognostic models in DILI is not a novelty. Back in 2014, Chen *et al.* reviewed the methodologies and limitations in the construction of models able to predict DILI risk in humans [138]. In this work, the authors foresaw some advances in DILI research that, nowadays, with a better understanding of the pathophysiology of DILI and improved bioinformatics capabilities, allow to partially deal with some of the listed shortcomings.

AI modelling is founded on the design of algorithms that need to be *fed* with data. In this manner, the rapid advances in the field of omics, a broad term that encompasses the genome, transcriptome, metabolome, proteome, and microbiome, have contributed to foster the development of analytical *big data* methodologies aimed to identify, as mentioned above, genetic markers of susceptibility to DILI, or unveil new mechanistic pathways of the disease [139]. Furthermore, the growing availability of real-world data, i.e., robust clinical information retrieved from the electronic health records or digital health devices [140] (digitized histology – mentioned above), yields an opportunity to integrate both omics and non-omics data to provide a holistic perspective of such a complex condition as DILI [141]. This is an appealing approach to be developed in the upcoming years that will lead to the improvement of patient risk stratification through the use of powerful analytical methodologies able to process massive amounts of data, and the implementation of tools in clinical practice to boost the transition towards precision personalized medicine.

5. Networking and regulatory aspects

5.1. EASL DHILI Consortium

Considering the low population prevalence of DILI with a large number of causative agents, international collaboration involving investigators from diverse disciplines is crucial for the conduct and delivery of definitive research studies. The Prospective European Drug-Induced Liver Injury Network (ProEuroDILINet) enabled establishment of a European 'leading expert network' on DILI. This initiative brings together researchers from different fields providing outreach to other European scientific societies and groups to promote collaboration on areas of common interest in DILI. Building on this multidisciplinary collaborative approach of ProEuroDILINet, the **D**rug and **H**erbal & Dietary Supplement-**I**nduced **L**iver **I**njury" **(DHILI)** consortium has been established. This has been endorsed by **EASL** (European Association for the Study of the Liver) and will ensure the continuity of a robust DILI network. Here we aim to facilitate, amongst others, events, educational activities, involvement in EASL International Liver Conference programming, and the proposal of an EASL Monothematic Conferences on DHILI (https://easldhiliconsortium.eu/). The framework created by the Consortium is the ideal environment to facilitate interaction between industry, academia, basic scientists, clinicians, and regulatory authorities and to encourage joint scientific meetings. Adoption of consistent and evidence-based policies by regulatory authorities will increase public assurance of drug safety, as well as in herbal and dietary supplements. The International Consortium for Innovation and Quality in Pharmaceutical Development, the IQ DILI Initiative, is catalyzing new collaborations to build consensus and propose best practice on issues encompassing DILI [14,142]. Harmonization of terminology for DILI in general and for liver injury attributed to HDS is essential to gain further knowledge about DILI across countries and continents. Indeed, the DILI case definition and severity grading developed by DILI experts has been used in most DILI studies for over a decade [143].

In the absence of prognostic biomarkers, the pharmaceutical industry relies heavily on the original Zimmerman definition of hepatocellular jaundice (aka Hy's Law) to predict DILI fatality risk in drug development. However, Zimmerman's observation was solely based on retrospective analysis of post-marketing cases [144], whilst an acceptable alkaline phosphatase level to identify hepatocellular injury is not clearly defined by Zimmerman or regulatory guidance [145]. An example of multilateral collaboration is the proposal to test the performance of the new R based Hy's law, which is intended to minimize confusion about cholestatic vs hepatocellular DILI by testing objective liver enzyme cut-off values (new R value based on ALT or AST whichever higher) [146,147]. The new R was also developed in the post-marketing setting but could prove useful in drug development, as a more objective and uniform criterion, outperform classic Hy's law criteria, which has never been validated in the pre-market or preclinical setting but is still recommended in the current FDA Guidance.

This would also be the case if effective biomarkers were to be developed to properly characterize DI-ALH cases that occur during clinical development, as this diagnosis may imply long-term monitoring strategies. To achieve this goal, a public-private partnership and the sharing of clinical and biological samples by partner companies would be required [18].

Furthermore, there is a need for developing strategies to involve patients who have suffered DILI and to provide public education to prioritize research questions in the DILI field, identify gaps in clinical service relevant to DILI subjects and improve public awareness.

5.2. Criteria to appoint centers as networks of excellence

A milestone for the DHILI Consortium will be the creation of EASL **Clinical Centres of Excellence in DHILI**, in line with its mission to improve the quality of life and reduce morbidity and mortality for as many people as possible by improving liver health. In general, to be designated as an EASL Centre of Excellence in DHILI, centers should provide hepatobiliary services, including: Pathway for Acute Liver/Biliary Injury, Pathway for Jaundice and regular clinical pathology conferences. It should also have access to the investigations necessary to assess suspected DHILI, research interests, projects, and publications in the field of DHILI, and teaching and training programs in hepatobiliary medicine. Finally, these centres would contribute to substantial influence on professional societies, regulatory agencies, and policy makers.

5.3. Proof of concept, mechanistic, targeted oriented Clinical Trials in DILI

While DILI carries significant morbidity and mortality, there is no available treatment with demonstrated efficacy other than withdrawing the suspected offending chemical agent and providing supportive care [15,148]. Therefore, identifying an effective therapy for DILI is a high clinical priority. In daily clinical practice, clinicians occasionally prescribe steroids to treat DILI and accompanying extrahepatic manifestations, but systematic studies evaluating corticosteroid use in patients with suspected idiosyncratic DILI have not been carried out so far. Recently, in a propensity score-matched analysis, corticosteroid administration was associated with a greater rate of normalization of liver enzymes in patients with serious DILI [149]. This study provides a robust rationale for further investigating the use of corticosteroids in DILI. There is also an urgent need to establish relevant endpoints to

assess the efficacy of novel interventions or to explore novel biomarkers to advance the approach to precision medicine in DILI [150]. In parallel, it will enable the study of DILI pathogenesis, the mechanisms involved in response to therapy and potentially the identification of new patient-specific druggable targets.

6. Summary

This proposed operational framework will pave the way for the advancement of DILI research and may lead to a paradigm shift towards a more holistic approach that integrates basic, applied, translational and clinical research into the disease. The Roadmap's objectives are to identify key challenges, define a shared vision across all stakeholders, and provide opportunities to overcome basic and translational gaps through implementation of high-quality research programs to achieve progress and impact on healthcare practice in the field of DILI.

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Author statement

The work has not been published previously, it is not under consideration for publication elsewhere, and it has been reviewed and approved by all authors. If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Declaration of Competing Interest

The authors have no conflict of interest to disclose in relation to this topic.

Data Availability

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References

[1] R.J. Andrade, N.P. Chalasani, E.S. Björnsson, A. Suzuki, G.A. Kullak-Ublick, P. B. Watkins, H. Devarbhavi, M. Merz, M.I. Lucena, N. Kaplowitz, G.P. Aithal, Drug-induced liver injury, Nat. Rev. Dis. Prim. 5 (1) (2019) 22, https://doi.org/10.1038/s41572-019-0105-0.

[2] E.S. Björnsson, O.M. Bergmann, H.K. Björnsson, R.B. Kvaran, S. Olafsson, Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland, Gastroenterology 144 (7) (2013) 1419–1420, https://doi.org/10.1053/j.gastro.2013.02.006.

[3] H. Hussaini, C.S. O'Brien, E.J. Despott, H.R. Dalton, Antibiotic therapy: a major cause of drug-induced jaundice in southwest England, Eur. J. Gastroenterol. Hepatol. 19 (1) (2007) 15–20, https://doi.org/10.1097/01.meg.0000250581.77865.68.

[4] A. Reuben, D.G. Koch, W.M. Lee, Drug-induced acute liver failure: results of a U. S. multicenter, prospective study, Hepatology 52 (6) (2010) 2065–2076, https://doi.org/10.1002/hep.23937.

[5] M. García-Cortés, M. Robles-Diaz, C. Stephens, A. Ortega-Alonso, M.I. Lucena, R. J. Andrade, Drug induced liver injury: an update, Arch. Toxicol. 94 (2020) 3381–3407, https://doi.org/10.1007/s00204-020-02885-1.

[6] C. Stephens, M. Robles-Díaz, I. Medina-Cáliz, M. García-Cortés, A. Ortega-Alonso, J. Sanabria-Cabrera, A. Gonzalez-Jimenez, I. Álvarez-Álvarez, M. Slim, M. Jimenez-Perez, R. Gonzalez-Grande, M.C. Fernandez, M. Casado, G. Soriano, E. Román, H. Hallal, M. Romero-Gomez, A. Castiella, I. Conde, M. Prieto, J. M. Moreno-Planas, A. Giraldez, J.M. Moreno-Sanfiel, N. Kaplowitz, M.I. Lucena, R.J. Andrade, Comprehensive analysis and insights gained from long-term experience of the Spanish DILI Registry, J. Hepatol. 75 (1) (2021) 86–97, https://doi.org/10.1016/j.jhep.2021.01.029.

[7] E.S. Björnsson, C. Stephens, E. Atallah, M. Robles-Diaz, I. Álvarez-Álvarez, A. Gerbes, S. Weber, G. Stirnimann, G. Kullak-Ublick, H. Cortez-Pinto, J.I. Grove, M.I. Lucena, R.J. Andrade, G.P. Aithal, A new framework for advancing in drug-induced liver injury research. The prospective European DILI registry, Liver Int 43 (1) (2023) 115–126, https://doi.org/10.1111/liv.15378.

[8] H. Olson, G. Betton, D. Robinson, K. Thomas, A. Monro, G. Kolaja, P. Lilly, J. Sanders, G. Sipes, W. Bracken, M. Dorato, K. Van Deun, P. Smith, B. Berger, A. Heller, Concordance of the toxicity of pharmaceuticals in humans and in animals, Regul. Toxicol. Pharmacol. 32 (1) (2000) 56–67, https://doi.org/10.1006/rtph.2000.1399.

[9] G.A. Kullak-Ublick, R.J. Andrade, M. Merz, P. End, A. Benesic, A.L. Gerbes, G. P. Aithal, Drug-induced liver injury: recent advances in diagnosis and risk assessment, Gut 66 (6) (2017) 1154–1164, https://doi.org/10.1136/gutjnl-2016-313369.

[10] J.C. Fernández-Checa, P. Bagnaninchi, H. Ye, P. Sancho-Bru, J.M. Falcon-Perez, F. Royo, C. Garcia-Ruiz, O. Konu, J. Miranda, O. Lunov, A. Dejneka, A. Elfick, A. McDonald, G.J. Sullivan, G.P. Aithal, M.I. Lucena, R.J. Andrade, B. Fromenty, M. Kranendonk, F.J. Cubero, L.J. Nelson, Advanced preclinical models for evaluation of drug-induced liver injury - consensus statement by the European Drug-induced liver injury network (ProEuroDILI Net), J. Hepatol. 75 (4) (2021) 935–959, https://doi.org/10.1016/j.jhep.2021.06.021.

[11] A. Segovia-Zafra, M. Villanueva-Paz, A. Serras, G. Matilla-Cabello, A. Bodoque-García, D. Di Zeo-Sánchez, H. Niu, I. Álvarez-Álvarez, S. Godek, I. Milisav, R.J. Andrade, M.I. Lucena, J.C. Fernández-Checa, F.J. Cubero, J. Miranda, L. Nelson, In vitro validation of drug-induced liver injury models with control compounds: A consensus-driven systematic review by the ProEuroDILI Network. *Under review: Nat. Commun.*

[12] European Association for the Study of the Liver (EASL), Clinical practice guidelines: drug-induced liver injury, J. Hepatol. 70 (6) (2019) 1222–1261, https://doi.org/10.1016/j.jhep.2019.02.014.

[13] Council for International Organizations of Medical Sciences (CIOMS), Drug-induced liver injury (DILI): current status and future directions for drug development and the post-market setting, A Consens. A CIOMS Work. Group (2020), https://doi.org/10.56759/ojsg8296.

[14] E. Cohen, M. Patwardhan, R. Raheja, D. Alpers, R.J. Andrade, M. Avigan, J. H. Lewis, D. Rockey, F. Chui, A. Iacob, C. Linardi, J. Shick, M.I. Lucena, Drug-induced liver injury (DILI) in the elderly. Consensus statements and recommendations from the IQ-DILI Consortium, Press.: Drug Saf. (2023).

[15] H. Niu, J. Sanabria-Cabrera, I. Álvarez-Álvarez, M. Robles-Díaz, S. Stankevičiūtė, G.P. Aithal, E.S. Björnsson, R.J. Andrade, M.I. Lucena, Prevention and management of idiosyncratic drug-induced liver injury: systematic review and meta-analysis of randomised clinical trials, 105404-105404, Pharmacol. Res. 164 (2021), https://doi.org/10.1016/j.phrs.2020.105404.

[16] M.I. Lucena, J. Sanabria, M. García-Cortes, C. Stephens, R.J. Andrade, Drug-induced liver injury in older people, Lancet Gastroenterol. Hepatol. 5 (9) (2020) 862–874, https://doi.org/10.1016/s2468-1253(20)30006-6.

[17] H. Niu, E. Atallah, I. Álvarez-Álvarez, I. Medina-Caliz, G.P. Aithal, C. Arikan, R. J. Andrade, M.I. Lucena, Therapeutic management of idiosyncratic drug-induced liver injury and acetaminophen hepatotoxicity in the paediatric population: a systematic review, Drug Saf. 45 (2022) 1329–1348, https://doi.org/10.1007/s40264-022-01224-w.

[18] R.J. Andrade, G.P. Aithal, Y.S. de Boer, R. Liberal, A.L. Gerbes, A. Regev, B. Beretta-Piccoli, C. Schramm, D.E. Kleiner, E. De Martin, G.A. Kullak-Ublick, G. Stirnimann, H. Devarbhavi, J.M. Vierling, M.P. Manns, M. Sebode, M. C. Londoño, M. Avigan, M. Robles-Diaz, M. García-Cortés, E. Atallah, M. Heneghan, N.P. Chalasani, P.J. Trivedi, P.H. Hayashi, R. Taubert, R. J. Fontana, S. Weber, Y.H. Oo, Y. Zen, A. Licata, M.I. Lucena, G. Mieli-Vergani, D. Vergani, E.S. Björnsson, Nomenclature, diagnosis and management of drug-

induced autoimmune-like hepatitis (DI-ALH): an expert opinion meeting report, J. Hepatol. 79 (3) (2023) 853–866, https://doi.org/10.1016/j.jhep.2023.04.033.
[19] E. Atallah, C. Freixo, I. Álvarez-Álvarez, F.J. Cubero, A.L. Gerbes, G.A. Kullak-Ublick, G.P. Aithal, Biomarkers of idiosyncratic drug-induced liver injury (DILI) - a systematic review, Expert. Opin. Drug. Metab. Toxicol. 17 (11) (2021) 1327–1343, https://doi.org/10.1080/17425255.2021.1999410.
[20] K.C. Ravindra, V.S. Vaidya, Z. Wang, J.D. Federspiel, R. Virgen-Slane, R. A. Everley, J.I. Grove, C. Stephens, M.F. Ocana, M. Robles-Diaz, M.I. Lucena, R. J. Andrade, E. Atallah, A.L. Gerbes, S. Weber, H. Cortez-Pinto, A.J. Fowell, H. Hussaini, E.S. Björnsson, J. Patel, G. Stirnimann, S. Verma, A.M. Elsharkawy, W.J.H. Griffiths, C. Hyde, J.W. Dear, G.P. Aithal, S.K. Ramaiah, Tandem mass tag-based quantitative proteomic profiling identifies candidate serum biomarkers of drug-induced liver injury in humans, 1215-1215, Nat. Commun. 14 (1) (2023), https://doi.org/10.1038/s41467-023-36858-6.
[21] N. Chalasani, H.L. Bonkovsky, R. Fontana, W. Lee, A. Stolz, J. Talwalkar, K. R. Reddy, P.B. Watkins, V. Navarro, H. Barnhart, J. Gu, J. Serrano, Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study, Gastroenterology 148 (7) (2015) 1340–1352, https://doi.org/10.1053/j.gastro.2015.03.006.
[22] H. Devarbhavi, M. Ghabril, H. Barnhart, M. Patil, S. Raj, J. Gu, N. Chalasani, H. L. Bonkovsky, Leflunomide-induced liver injury: differences in characteristics and outcomes in Indian and US registries, Liver Int 42 (6) (2022) 1323–1329, https://doi.org/10.1111/liv.15189.
[23] F. Bessone, N. Hernandez, M.I. Lucena, R.J. Andrade, The Latin American DILI registry experience: a successful ongoing collaborative strategic initiative, 313-313, Int. J. Mol. Sci. 17 (3) (2016), https://doi.org/10.3390/ijms17030313.
[24] J.I. Grove, C. Stephens, M.I. Lucena, R.J. Andrade, S. Weber, A. Gerbes, E. S. Bjornsson, G. Stirnimann, A.K. Daly, M. Hackl, K. Khamina-Kotisch, J.J. G. Marin, M.J. Monte, S.A. Paciga, M. Lingaya, S.S. Forootan, C.E.P. Goldring, O. Poetz, R. Lombaard, A. Stege, H.K. Bjorrnsson, M. Robles-Diaz, D. Li, T.D. B. Tran, S.K. Ramaiah, S.L. Samodelov, G.A. Kullak-Ublick, G.P. Aithal, c. on behalf of the TransBioLine, Study design for development of novel safety biomarkers of drug-induced liver injury by the translational safety biomarker pipeline (TransBioLine) consortium: a study protocol for a nested case–control study, Diagn. Progn. Res. 7 (1) (2023) 18, https://doi.org/10.1186/s41512-023-00155-z.
[25] R.J. Fontana, P.B. Watkins, H.L. Bonkovsky, N. Chalasani, T. Davern, J. Serrano, J. Rochon, Drug-induced liver injury network (DILIN) prospective study: rationale, design and conduct, Drug Saf. 32 (1) (2009) 55–68, https://doi.org/10.2165/00002018-200932010-00005.
[26] M. García-Cortés, C. Stephens, M.I. Lucena, A. Fernández-Castañer, R.J. Andrade, Causality assessment methods in drug induced liver injury: strengths and weaknesses, J. Hepatol. 55 (3) (2011) 683–691, https://doi.org/10.1016/j.jhep.2011.02.007.
[27] P.H. Hayashi, M.I. Lucena, R.J. Fontana, E.S. Bjornsson, G.P. Aithal, H. Barnhart, A. Gonzalez-Jimenez, Q. Yang, J. Gu, R.J. Andrade, J.H. Hoofnagle, A revised electronic version of RUCAM for the diagnosis of DILI, Hepatology 76 (1) (2022) 18–31, https://doi.org/10.1002/hep.32327.
[28] E. Atallah, S.J. Welsh, B. O'Carrigan, A. Oshaughnessy, I. Dolapo, A.S. Kerr, J. Kucharczak, C.Y.C. Lee, C. Crooks, A. Hicks, C.R. Chimakurthi, A. Rao, H. Franks, P.M. Patel, G.P. Aithal, Incidence, risk factors and outcomes of checkpoint inhibitor-induced liver injury: a 10-year real-world retrospective cohort study, JHEP Rep. 5 (10) (2023) 100851, https://doi.org/10.1016/j.jhepr.2023.100851.
[29] E. De Martin, J.M. Michot, O. Rosmorduc, C. Guettier, D. Samuel, Liver toxicity as a limiting factor to the increasing use of immune checkpoint inhibitors, JHEP Rep. 2 (6) (2020) 100170, https://doi.org/10.1016/j.jhepr.2020.100170.
[30] E.S. Björnsson, J. Talwalkar, S. Treeprasertsuk, P.S. Kamath, N. Takahashi, S. Sanderson, M. Neuhauser, K. Lindor, Drug-induced autoimmune hepatitis: clinical characteristics and prognosis, Hepatology 51 (6) (2010) 2040–2048, https://doi.org/10.1002/hep.23588.
[31] E.S. Björnsson, O.M. Bergmann, J.G. Jonasson, G. Grondal, B. Gudbjornsson, S. Olafsson, Drug-induced autoimmune hepatitis: Response to corticosteroids and lack of relapse after cessation of steroids, Clin. Gastroenterol. Hepatol. 15 (10) (2017) 1635–1636, https://doi.org/10.1016/j.cgh.2017.05.027.
[32] M. García-Cortés, A. Ortega-Alonso, G. Matilla-Cabello, I. Medina-Caliz, A. Castiella, I. Conde, E. Bonilla-Toyos, J. Pinazo, N. Hernandez, M. Tagle, V. Nunes, R. Parana, F. Bessone, N. Kaplowitz, M.I. Lucena, I. Álvarez-Álvarez, M. Robles-Diaz, R.J. Andrade, Clinical presentation, causative drugs and outcome of patients with autoimmune features in two prospective DILI registries, Liver Int (2023) 1–12, https://doi.org/10.1111/liv.15623.
[33] G. Codoni, T. Kirchner, B. Engel, A.M. Villamil, C. Efe, A.F. Stättermayer, J. P. Weltzsch, M. Sebode, C. Bernsmeier, A. Lleo, T.J. Gevers, L. Kupčinskas, A. Castiella, J. Pinazo, E. De Martin, I. Bobis, T.D. Sandahl, F. Pedica, F. Invernizzi, P. Del Poggio, T. Bruns, M. Kolev, N. Semmo, F. Bessone, B. Giguet, G. Poggi, M. Ueno, H. Jang, G. Elpek, N.K. Soylu, A. Cerny, H. Wedemeyer, D. Vergani, G. Mieli-Vergani, M.I. Lucena, R.J. Andrade, Y. Zen, R. Taubert, B. Terziroli Beretta-Piccoli, Histological and serological features of acute liver injury after SARS-CoV-2 vaccination, 100605-100605, JHEP Rep. 5 (1) (2022), https://doi.org/10.1016/j.jhepr.2022.100605.
[34] A. Di Giorgio, E. Bartolini, P.L. Calvo, M. Cananzi, F. Cirillo, C. Della Corte, C. Dionisi-Vici, G. Indolfi, R. Iorio, G. Maggiore, C. Mandato, G. Nebbia, E. Nicastro, M. Pinon, G. Ranucci, M. Sciveres, P. Vajro, L. D'Antiga, Diagnostic approach to acute liver failure in children: a position paper by the SIGENP Liver Disease Working Group, Dig. Liver Dis. 53 (5) (2021) 545–557, https://doi.org/10.1016/j.dld.2021.03.004.
[35] A. Alhadab, H. AlShihabi, F. Mohamed, Z. AlDuhilib, Z. Arain, R. Bader, Pediatric acute liver failure in Saudi Arabia: prognostic indicators, outcomes and the role of genetic testing, Eur. J. Gastroenterol. Hepatol. 35 (4) (2023) 420–430, https://doi.org/10.1097/MEG.0000000000002499.
[36] P. Nicoletti, S. Barrett, L. McEvoy, A.K. Daly, G. Aithal, M.I. Lucena, R.J. Andrade, M. Wadelius, P. Hallberg, C. Stephens, E.S. Bjornsson, P. Friedmann, K. Kainu, T. Laitinen, A. Marson, M. Molokhia, E. Phillips, W. Pichler, A. Romano, N. Shear, G. Sills, L.K. Tanno, A. Swale, A. Floratos, Y. Shen, M.R. Nelson, P.B. Watkins, M. J. Daly, A.P. Morris, A. Alfirevic, M. Pirmohamed, Shared genetic risk factors across carbamazepine-induced hypersensitivity reactions, Clin. Pharmacol. Ther. 106 (5) (2019) 1028–1036, https://doi.org/10.1002/cpt.1493.
[37] T. Mitra-Ghosh, S.P. Callisto, J.K. Lamba, R.P. Remmel, A.K. Birnbaum, J. M. Barbarino, T.E. Klein, R.B. Altman, PharmGKB summary: lamotrigine pathway, pharmacokinetics and pharmacodynamics, Pharm. Genom. 30 (4) (2020) 81–90, https://doi.org/10.1097/FPC.0000000000000397.
[38] F. DiPaola, J.P. Molleston, J. Gu, E.T. Cirulli, N. Chalasani, H. Barnhart, D. E. Kleiner, J.H. Hoofnagle, R.J. Fontana, Antimicrobials and antiepileptics are the leading causes of idiosyncratic drug-induced liver injury in american children, J. Pediatr. Gastroenterol. Nutr. 69 (2) (2019) 152–159, https://doi.org/10.1097/mpg.0000000000002383.
[39] I. Medina-Cáliz, M. García-Cortés, A. Gonzalez-Jimenez, M.R. Cabello, M. Robles-Diaz, J. Sanabria-Cabrera, R. Sanjuan-Jimenez, A. Ortega-Alonso, B. García-Muñoz, I. Moreno, M. Jimenez-Perez, M.C. Fernandez, P. Ginés, M. Prieto, I. Conde, H. Hallal, G. Soriano, E. Roman, A. Castiella, E. Blanco-Reina, M. R. Montes, M. Quiros-Cano, F. Martin-Reyes, M.I. Lucena, R.J. Andrade, Herbal and dietary supplement-induced liver injuries in the Spanish DILI Registry, Clin. Gastroenterol. Hepatol. 16 (9) (2018) 1495–1502, https://doi.org/10.1016/j.cgh.2017.12.051.
[40] F. Bessone, M. García-Cortés, I. Medina-Caliz, N. Hernandez, R. Parana, M. Mendizabal, M.I. Schinoni, E. Ridruejo, V. Nunes, M. Peralta, G. Santos, M. Anders, D. Chiodi, M. Tagle, P. Montes, E. Carrera, M. Arrese, M.I. Lizarzabal, I. Álvarez-Álvarez, E. Caballano-Infantes, H. Niu, J. Pinazo, M.R. Cabello, M. I. Lucena, R.J. Andrade, Herbal and dietary supplements-induced liver injury in Latin America: experience from the LATINDILI network, Clin. Gastroenterol. Hepatol. 20 (3) (2022) e548–e563, https://doi.org/10.1016/j.cgh.2021.01.011.
[41] M. Ghabril, J. Ma, K.R. Patidar, L. Nephew, A.P. Desai, E.S. Orman, R. Vuppalanchi, S. Kubal, N. Chalasani, Eight-fold increase in dietary supplement-related liver failure leading to transplant waitlisting over the last quarter century in the United States, Liver Transpl. 28 (2) (2022) 169–179, https://doi.org/10.1002/lt.26246.
[42] V. Kesar, L. Channen, U. Masood, P. Grewal, J. Ahmad, N.C. Roth, J.A. Odin, Liver transplantation for acute liver injury in asians is more likely due to herbal and dietary supplements, Liver Transpl. 28 (2) (2022) 188–199, https://doi.org/10.1002/lt.26260.
[43] G.P. Aithal, Speaking of the (barely legal) elephant in the room: herbal or dietary supplement-related acute liver failure, Liver Transpl. 28 (2) (2022) 159–160, https://doi.org/10.1002/lt.26377.
[44] J.H. Hoofnagle, H.L. Bonkovsky, E.J. Phillips, Y.J. Li, J. Ahmad, H. Barnhart, F. Durazo, R.J. Fontana, J. Gu, I. Khan, D.E. Kleiner, C. Koh, D.C. Rockey, L. B. Seeff, J. Serrano, A. Stolz, H.L. Tillmann, R. Vuppalanchi, V.J. Navarro, HLA-B*35:01 and green tea-induced liver injury, Hepatology 73 (6) (2021) 2484–2493, https://doi.org/10.1002/hep.31538.
[45] C. Li, T. Rao, X. Chen, Z. Zou, A. Wei, J. Tang, P. Xiong, P. Li, J. Jing, T. He, Z. Bai, J. Yin, Z. Tan, P. Yu, H. Zhou, J. Wang, X. Xiao, D. Ouyang, HLA-B*35:01 allele is a potential biomarker for predicting polygonum multiflorum-induced liver injury in humans, Hepatology 70 (1) (2019) 346–357, https://doi.org/10.1002/hep.30660.
[46] G.P. Aithal, Of potions, poisons, polygonum, and pre-emptive polymorphism, Hepatology 70 (1) (2019) 8–10, https://doi.org/10.1002/hep.30798.
[47] R.J. Fontana, E.S. Björnsson, R. Reddy, R.J. Andrade, The evolving profile of idiosyncratic drug-induced liver injury, Clin. Gastroenterol. Hepatol. 21 (8) (2023) 2088–2099, https://doi.org/10.1016/j.cgh.2022.12.040.
[48] E.S. Björnsson, R.J. Andrade, Long-term sequelae of drug-induced liver injury, J. Hepatol. 76 (2) (2022) 435–445, https://doi.org/10.1016/j.jhep.2021.10.011.
[49] I. Medina-Cáliz, M. Robles-Díaz, B. García-Muñoz, C. Stephens, A. Ortega-Alonso, M. García-Cortés, A. González-Jimenez, J.A. Sanabria-Cabrera, I. Moreno, M. C. Fernandez, M. Romero-Gomez, J.M. Navarro, A.M. Barriocanal, E. Montane, H. Hallal, S. Blanco, G. Soriano, E.M. Roman, E. Gómez-Dominguez, A. Castiella, E.M. Zapata, M. Jimenez-Perez, J.M. Moreno, A. Aldea-Perona, M. Hernández-Guerra, M. Prieto, M.E. Zoubek, N. Kaplowitz, M.I. Lucena, R.J. Andrade, Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury, J. Hepatol. 65 (3) (2016) 532–542, https://doi.org/10.1016/j.jhep.2016.05.003.
[50] H.L. Bonkovsky, D.E. Kleiner, J. Gu, J.A. Odin, M.W. Russo, V.M. Navarro, R. J. Fontana, M.S. Ghabril, H. Barnhart, J.H. Hoofnagle, Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements, Hepatology 65 (4) (2017) 1267–1277, https://doi.org/10.1002/hep.28967.
[51] M. Chen, A. Suzuki, J. Borlak, R.J. Andrade, M.I. Lucena, Drug-induced liver injury: interactions between drug properties and host factors, J. Hepatol. 63 (2) (2015) 503–514, https://doi.org/10.1016/j.jhep.2015.04.016.
[52] A.C. Cheung, D.I. Walker, B.D. Juran, G.W. Miller, K.N. Lazaridis, Studying the exposome to understand the environmental determinants of complex liver diseases, Hepatology 71 (1) (2020) 352–362, https://doi.org/10.1002/hep.31028.
[53] D.I. Walker, B.D. Juran, A.C. Cheung, E.M. Schlicht, Y. Liang, M. Niedzwiecki, N. F. LaRusso, G.J. Gores, D.P. Jones, G.W. Miller, K.N. Lazaridis, High-resolution

exposomics and metabolomics reveals specific associations in cholestatic liver diseases, Hepatol. Commun. 6 (5) (2022) 965–979, https://doi.org/10.1002/hep4.1871.
[54] P.J. Lioy, S.M. Rappaport, Exposure science and the exposome: an opportunity for coherence in the environmental health sciences, Environ. Health Perspect. 119 (2011) A466–A467, https://doi.org/10.1289/ehp.1104387.
[55] S.M. Rappaport, Implications of the exposome for exposure science, J. Expo. Sci. Environ. Epidemiol. 21 (1) (2011) 5–9, https://doi.org/10.1038/jes.2010.50.
[56] A. Suzuki, E.M. Brunt, D.E. Kleiner, R. Miquel, T.C. Smyrk, R.J. Andrade, M. I. Lucena, A. Castiella, K. Lindor, E.S. Björnsson, The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis vs drug-induced liver injury, Hepatology 54 (3) (2011) 931–939, https://doi.org/10.1002/hep.24481.
[57] J. Ahmad, H. Barnhart, M. Bonacini, M. Ghabril, P.H. Hayashi, J.A. Odin, D. C. Rockey, S. Rossi, J. Serrano, H.L. Tillmann, D.E. Kleiner, Value of liver biopsy in the diagnosis of drug-induced liver injury, J. Hepatol. 76 (5) (2022) 1070–1078, https://doi.org/10.1016/j.jhep.2021.12.043.
[58] I. García-Ruiz, P. Solís-Muñoz, D. Fernández-Moreira, T. Muñoz-Yagüe, J.A. Solís-Herruzo, In vitro treatment of HepG2 cells with saturated fatty acids reproduces mitochondrial dysfunction found in nonalcoholic steatohepatitis, Dis. Model. Mech. 8 (2) (2015) 183–191, https://doi.org/10.1242/dmm.018234.
[59] K. Takahashi, K. Tanabe, M. Ohnuki, M. Narita, T. Ichisaka, K. Tomoda, S. Yamanaka, Induction of pluripotent stem cells from adult human fibroblasts by defined factors, Cell 131 (5) (2007) 861–872, https://doi.org/10.1016/j.cell.2007.11.019.
[60] A.K. Daly, Using genome-wide association studies to identify genes important in serious adverse drug reactions, Annu. Rev. Pharmacol. Toxicol. 52 (1) (2012) 21–35, https://doi.org/10.1146/annurev-pharmtox-010611-134743.
[61] M. Koido, E. Kawakami, J. Fukumura, Y. Noguchi, M. Ohori, Y. Nio, P. Nicoletti, G.P. Aithal, A.K. Daly, P.B. Watkins, H. Anayama, Y. Dragan, T. Shinozawa, T. Takebe, Polygenic architecture informs potential vulnerability to drug-induced liver injury, Nat. Med. 26 (10) (2020) 1541–1548, https://doi.org/10.1038/s41591-020-1023-0.
[62] Y. Shi, H. Inoue, J.C. Wu, S. Yamanaka, Induced pluripotent stem cell technology: a decade of progress, Nat. Rev. Drug Discov. 16 (2) (2017) 115–130, https://doi.org/10.1038/nrd.2016.245.
[63] P. Roelandt, J. Vanhove, C. Verfaillie, Directed differentiation of pluripotent stem cells to functional hepatocytes, Methods Mol. Biol. 997 (2013) 141–147, https://doi.org/10.1007/978-1-62703-348-0_11.
[64] T. Shinozawa, M. Kimura, Y. Cai, N. Saiki, Y. Yoneyama, R. Ouchi, H. Koike, M. Maezawa, R.R. Zhang, A. Dunn, A. Ferguson, S. Togo, K. Lewis, W. L. Thompson, A. Asai, T. Takebe, High-Fidelity drug-induced liver injury screen using human pluripotent stem cell-derived organoids, Gastroenterology 160 (3) (2021) 831–846, https://doi.org/10.1053/j.gastro.2020.10.002.
[65] C.J. Zhang, S.R. Meyer, M.J. O'Meara, S. Huang, M.M. Capeling, D. Ferrer-Torres, C.J. Childs, J.R. Spence, R.J. Fontana, J.Z. Sexton, A human liver organoid screening platform for DILI risk prediction, J. Hepatol. 78 (5) (2023) 998–1006, https://doi.org/10.1016/j.jhep.2023.01.019.
[66] M.T. Donato, L. Tolosa, Stem-cell derived hepatocyte-like cells for the assessment of drug-induced liver injury, Differentiation 106 (2019) 15–22, https://doi.org/10.1016/j.diff.2019.02.004.
[67] R. Boon, M. Kumar, T. Tricot, I. Elia, L. Ordovas, F. Jacobs, J. One, J. De Smedt, G. Eelen, M. Bird, P. Roelandt, G. Doglioni, K. Vriens, M. Rossi, M.A. Vazquez, T. Vanwelden, F. Chesnais, A. El Taghdouini, M. Najimi, E. Sokal, D. Cassiman, J. Snoeys, M. Monshouwer, W.S. Hu, C. Lange, P. Carmeliet, S.M. Fendt, C. M. Verfaillie, Amino acid levels determine metabolism and CYP450 function of hepatocytes and hepatoma cell lines, Nat. Commun. 11 (1) (2020) 1393, https://doi.org/10.1038/s41467-020-15058-6.
[68] T. Tricot, H.J. Thibaut, K. Abbasi, R. Boon, N. Helsen, M. Kumar, J. Neyts, C. Verfaillie, Metabolically improved stem cell derived hepatocyte-like cells support HBV life cycle and are a promising tool for HBV studies and antiviral drug screenings, Biomedicines 10 (2) (2022) 268, https://doi.org/10.3390/biomedicines10020268.
[69] R.M. Florentino, K. Morita, N. Haep, T. Motomura, R. Diaz-Aragon, L.A. P. Faccioli, A. Collin de l'Hortet, Z. Cetin, C. Frau, L. Vernetti, A.K. Amler, A. Thomas, T. Lam, L. Kloke, K. Takeishi, D.L. Taylor, I.J. Fox, A. Soto-Gutierrez, Biofabrication of synthetic human liver tissue with advanced programmable functions, iScience 25 (12) (2022) 105503, https://doi.org/10.1016/j.isci.2022.105503.
[70] F. Tasnim, J. Xing, X. Huang, S. Mo, X. Wei, M.H. Tan, H. Yu, Generation of mature kupffer cells from human induced pluripotent stem cells, Biomaterials 192 (2019) 377–391, https://doi.org/10.1016/j.biomaterials.2018.11.016.
[71] J. Vallverdu, R.A. Martinez, I. Mannaerts, S. Verhulst, A. Smout, M. Coll, S. Arino, T. Rubio-Tomas, B. Aguilar-Bravo, C. Martinez-Sanchez, D. Blaya, C.M. Verfaillie, L.A. van Grunsven, P. Sancho-Bru, Directed differentiation of human induced pluripotent stem cells to hepatic stellate cells, Nat. Protoc. 16 (5) (2021) 2542–2563, https://doi.org/10.1038/s41596-021-00509-1.
[72] D.E. Di Zeo-Sánchez, A. Segovia-Zafra, G. Matilla-Cabello, J.M. Pinazo-Bandera, R.J. Andrade, M.I. Lucena, M. Villanueva-Paz, Modeling drug-induced liver injury: current status and future prospects, Expert. Opin. Drug Metab. Toxicol. 18 (9) (2022) 555–573, https://doi.org/10.1080/17425255.2022.2122810.
[73] X. Zhang, T. Jiang, D. Chen, Q. Wang, L.W. Zhang, Three-dimensional liver models: state of the art and their application for hepatotoxicity evaluation, Crit. Rev. Toxicol. 50 (4) (2020) 279–309, https://doi.org/10.1080/10408444.2020.1756219.
[74] A.S. Serras, J.S. Rodrigues, M. Cipriano, A.V. Rodrigues, N.G. Oliveira, J. P. Miranda, A critical perspective on 3D liver models for drug metabolism and toxicology studies, Front. Cell Dev. Biol. 9 (2021) 626805, https://doi.org/10.3389/fcell.2021.626805.
[75] S.H. Saxton, K.R. Stevens, 2D and 3D liver models, J. Hepatol. 78 (4) (2023) 873–875, https://doi.org/10.1016/j.jhep.2022.06.022.
[76] S. Yang, M. Ooka, R.J. Margolis, M. Xia, Liver three-dimensional cellular models for high-throughput chemical testing, Cell Rep. Methods 3 (3) (2023) 100432, https://doi.org/10.1016/j.crmeth.2023.100432.
[77] A. Segovia-Zafra, D.E. Di Zeo-Sanchez, C. Lopez-Gomez, Z. Perez-Valdes, E. Garcia-Fuentes, R.J. Andrade, M.I. Lucena, M. Villanueva-Paz, Preclinical models of idiosyncratic drug-induced liver injury (iDILI): moving towards prediction, Acta Pharm. Sin. B 11 (12) (2021) 3685–3726, https://doi.org/10.1016/j.apsb.2021.11.013.
[78] R. Ouchi, S. Togo, M. Kimura, T. Shinozawa, M. Koido, H. Koike, W. Thompson, R.A. Karns, C.N. Mayhew, P.S. McGrath, H.A. McCauley, R.R. Zhang, K. Lewis, S. Hakozaki, A. Ferguson, N. Saiki, Y. Yoneyama, I. Takeuchi, Y. Mabuchi, C. Akazawa, H.Y. Yoshikawa, J.M. Wells, T. Takebe, Modeling steatohepatitis in humans with pluripotent stem cell-derived organoids, Cell Metab. 30 (2) (2019) 374–384, https://doi.org/10.1016/j.cmet.2019.05.007.
[79] M.J. Gomez-Lechon, L. Tolosa, Human hepatocytes derived from pluripotent stem cells: a promising cell model for drug hepatotoxicity screening, Arch. Toxicol. 90 (9) (2016) 2049–2061, https://doi.org/10.1007/s00204-016-1756-1.
[80] S. Rajasekar, D.S.Y. Lin, F. Zhang, A. Sotra, A. Boshart, S. Clotet-Freixas, A. Liu, J. A. Hirota, S. Ogawa, A. Konvalinka, B. Zhang, Subtractive manufacturing with swelling induced stochastic folding of sacrificial materials for fabricating complex perfusable tissues in multi-well plates, Lab Chip 22 (10) (2022) 1929–1942, https://doi.org/10.1039/d1lc01141c.
[81] E.M. Wilson, J. Bial, B. Tarlow, G. Bial, B. Jensen, D.L. Greiner, M.A. Brehm, M. Grompe, Extensive double humanization of both liver and hematopoiesis in FRGN mice, Stem. Cell Res. 13 (3) (2014) 404–412, https://doi.org/10.1016/j.scr.2014.08.006.
[82] S. Torres, A. Baulies, N. Insausti-Urkia, C. Alarcón-Vila, R. Fucho, E. Solsona-Vilarrasa, S. Núñez, D. Robles, V. Ribas, L. Wakefield, M. Grompe, M.I. Lucena, R. J. Andrade, S. Win, T.A. Aung, N. Kaplowitz, C. García-Ruiz, J.C. Fernández-Checa, Endoplasmic reticulum stress-induced upregulation of STARD1 promotes acetaminophen-induced acute liver failure, Gastroenterology 157 (2) (2019) 552–568, https://doi.org/10.1053/j.gastro.2019.04.023.
[83] R. Fucho, E. Solsona-Vilarrasa, S. Torres, S. Nuñez, N. Insausti-Urkia, A. Edo, M. Calvo, A. Bosch, G. Martin, C. Enrich, C. García-Ruiz, J.C. Fernández-Checa, Zonal expression of StARD1 and oxidative stress in alcoholic-related liver disease, J. Lipid Res. 64 (8) (2023) 100413, https://doi.org/10.1016/j.jlr.2023.100413.
[84] E. Kaffe, M. Roulis, J. Zhao, R. Qu, E. Sefik, H. Mirza, J. Zhou, Y. Zheng, G. Charkoftaki, V. Vasiliou, D.F. Vatner, W.Z. Mehal, K. Yuval, R.A. Flavell, Humanized mouse liver reveals endothelial control of essential hepatic metabolic functions, Cell 186 (18) (2023) 3793–3809, https://doi.org/10.1016/j.cell.2023.07.017.
[85] A. Lorga, L. Dara, Cell death in drug-induced liver injury, Adv. Pharmacol. 85 (2019) 31–74, https://doi.org/10.1016/bs.apha.2019.01.006.
[86] C. Cai, H. Ma, J. Peng, X. Shen, X. Zhen, C. Yu, P. Zhang, F. Ji, J. Wang, USP25 regulates KEAP1-NRF2 anti-oxidation axis and its inactivation protects acetaminophen-induced liver injury in male mice, Nat. Commun. 14 (1) (2023) 3648, https://doi.org/10.1038/s41467-023-39412-6.
[87] F.J. Cubero, M.E. Zoubek, W. Hu, J. Peng, G. Zhao, Y.A. Nevzorova, M. Al Masaoudi, L.P. Bechmann, M.V. Boekschoten, M. Muller, C. Preisinger, N. Gassler, A.E. Canbay, T. Luedde, R.J. Davis, C. Liedtke, C. Trautwein, Combined activities of JNK1 and JNK2 in hepatocytes protect against toxic liver injury, Gastroenterology 150 (4) (2016) 968–981, https://doi.org/10.1053/j.gastro.2015.12.019.
[88] S. Win, T.A. Than, N. Kaplowitz, The regulation of JNK signaling pathways in cell death through the interplay with mitochondrial SAB and upstream post-translational effects, Int. J. Mol. Sci. 19 (11) (2018), https://doi.org/10.3390/ijms19113657.
[89] M. Marí, F. Caballero, A. Colell, A. Morales, J. Caballeria, A. Fernandez, C. Enrich, J.C. Fernández-Checa, C. García-Ruiz, Mitochondrial free cholesterol loading sensitizes to TNF- and Fas-mediated steatohepatitis, Cell Metab. 4 (3) (2006) 185–198, https://doi.org/10.1016/j.cmet.2006.07.006.
[90] J. Allard, D. Le Guillou, K. Begriche, B. Fromenty, Drug-induced liver injury in obesity and nonalcoholic fatty liver disease, Adv. Pharmacol. 85 (2019) 75–107, https://doi.org/10.1016/bs.apha.2019.01.003.
[91] S. Hassan, S. Sebastian, S. Maharjan, A. Lesha, A.M. Carpenter, X. Liu, X. Xie, C. Livermore, Y.S. Zhang, A. Zarrinpar, Liver-on-a-Chip models of fatty liver disease, Hepatology 71 (2) (2020) 733–740, https://doi.org/10.1002/hep.31106.
[92] M. Pelecha, E. Villanueva-Badenas, E. Timor-Lopez, M.T. Donato, L. Tolosa, Cell models and omics techniques for the study of nonalcoholic fatty liver disease: Focusing on stem cell-derived cell models, Antioxidants 11 (1) (2021), https://doi.org/10.3390/antiox11010086.
[93] M.J. Ramos, L. Bandiera, F. Menolascina, J.A. Fallowfield, In vitro models for non-alcoholic fatty liver disease: emerging platforms and their applications, iScience 25 (1) (2022) 103549, https://doi.org/10.1016/j.isci.2021.103549.
[94] M.C. Sinton, J. Meseguer-Ripolles, B. Lucendo-Villarin, S. Wernig-Zorc, J. P. Thomson, R.N. Carter, M.J. Lyall, P.D. Walker, A. Thakker, R.R. Meehan, G. G. Lavery, N.M. Morton, C. Ludwig, D.A. Tennant, D.C. Hay, A.J. Drake, A human pluripotent stem cell model for the analysis of metabolic dysfunction in hepatic steatosis, iScience 24 (1) (2021) 101931, https://doi.org/10.1016/j.isci.2020.101931.

[95] P.A. Soret, J. Magusto, C. Housset, J. Gautheron, In vitro and in vivo models of non-alcoholic fatty liver disease: a critical appraisal, J. Clin. Med. 10 (1) (2020), https://doi.org/10.3390/jcm10010036.
[96] J. Todoric, G. Di Caro, S. Reibe, D.C. Henstridge, C.R. Green, A. Vrbanac, F. Ceteci, C. Conche, R. McNulty, S. Shalapour, K. Taniguchi, P.J. Meikle, J. D. Watrous, R. Moranchel, M. Najhawan, M. Jain, X. Liu, T. Kisseleva, M.T. Diaz-Meco, J. Moscat, R. Knight, F.R. Greten, L.F. Lau, C.M. Metallo, M.A. Febbraio, M. Karin, Fructose stimulated de novo lipogenesis is promoted by inflammation, Nat. Metab. 2 (10) (2020) 1034–1045, https://doi.org/10.1038/s42255-020-0261-2.
[97] G. Cakan-Akdogan, A.M. Aftab, M.C. Cinar, K.A. Abdelhalim, O. Konu, Zebrafish as a model for drug induced liver injury: state of the art and beyond, Explor. Dig. Dis. 2 (2) (2023) 44–55, https://doi.org/10.37349/edd.2023.00017.
[98] A.D. Vliegenthart, C.S. Tucker, J. Del Pozo, J.W. Dear, Zebrafish as model organisms for studying drug-induced liver injury, Br. J. Clin. Pharmacol. 78 (6) (2014) 1217–1227, https://doi.org/10.1111/bcp.12408.
[99] S. Targen, O. Konu, Zebrafish xenotransplantation models for studying gene function and drug treatment in hepatocellular carcinoma, J. Gastrointest. Cancer 52 (4) (2021) 1248–1265, https://doi.org/10.1007/s12029-021-00782-z.
[100] X. Li, Y. Chen, X. Song, Y. Zhang, H. Li, Y. Zhao, The development and application of in silico models for drug induced liver injury, RSC Adv. 8 (15) (2018) 8101–8111, https://doi.org/10.1039/C7RA12957B.
[101] E. Arnesdotter, N. Spinu, J. Firman, D. Ebbrell, M.T.D. Cronin, T. Vanhaecke, M. Vinken, Derivation, characterisation and analysis of an adverse outcome pathway network for human hepatotoxicity, Toxicology 459 (2021) 152856, https://doi.org/10.1016/j.tox.2021.152856.
[102] X. Jia, X. Wen, D.P. Russo, L.M. Aleksunes, H. Zhu, Mechanism-driven modeling of chemical hepatotoxicity using structural alerts and an in vitro screening assay, J. Hazard. Mater. 436 (2022) 129193, https://doi.org/10.1016/j.jhazmat.2022.129193.
[103] C.V. Theodoris, L. Xiao, A. Chopra, M.D. Chaffin, Z.R. Al Sayed, M.C. Hill, H. Mantineo, E.M. Brydon, Z. Zeng, X.S. Liu, P.T. Ellinor, Transfer learning enables predictions in network biology, Nature 618 (7965) (2023) 616–624, https://doi.org/10.1038/s41586-023-06139-9.
[104] M. Rao, V. Nassiri, C. Alhambra, J. Snoeys, F. Van-Goethem, O. Irrechukwu, M. D. Aleo, H. Geys, K. Mitra, Y. Will, AI/ML models to predict the severity of drug-induced liver injury for small molecules, Chem. Res. Toxicol. 36 (7) (2023) 1129–1139, https://doi.org/10.1021/acs.chemrestox.3c00098.
[105] L.K.M. Shoda, J.L. Woodhead, S.Q. Siler, P.B. Watkins, B.A. Howell, Linking physiology to toxicity using DILIsym, a mechanistic mathematical model of drug-induced liver injury, Biopharm. Drug Dispos. 35 (1) (2014) 33–49, https://doi.org/10.1002/bdd.1878.
[106] K. Yang, J.L. Woodhead, P.B. Watkins, B.A. Howell, K.L. Brouwer, Systems pharmacology modeling predicts delayed presentation and species differences in bile acid-mediated troglitazone hepatotoxicity, Clin. Pharmacol. Ther. 96 (5) (2014) 589–598, https://doi.org/10.1038/clpt.2014.158.
[107] J.J. Beaudoin, W.J. Brock, P.B. Watkins, K.L.R. Brouwer, Quantitative systems toxicology modeling predicts that reduced biliary efflux contributes to tolvaptan hepatotoxicity, Clin. Pharmacol. Ther. 109 (2) (2021) 433–442, https://doi.org/10.1002/cpt.2007.
[108] V.V. Lakhani, G. Generaux, B.A. Howell, D.M. Longo, P.B. Watkins, Assessing liver effects of cannabidiol and valproate alone and in combination using quantitative systems toxicology, Clin. Pharmacol. Ther. 114 (5) (2023) 1006–1014, https://doi.org/10.1002/cpt.3004.
[109] N.S. Holman, M. Mosedale, K.K. Wolf, E.L. LeCluyse, P.B. Watkins, Subtoxic alterations in hepatocyte-derived exosomes: an early step in drug-induced liver injury? Toxicol. Sci. 151 (2) (2016) 365–375, https://doi.org/10.1093/toxsci/kfw047.
[110] F. Royo, K. Schlangen, L. Palomo, E. Gonzalez, J. Conde-Vancells, A. Berisa, A. M. Aransay, J.M. Falcon-Perez, Transcriptome of extracellular vesicles released by hepatocytes, PLoS One 8 (7) (2013) e68693, https://doi.org/10.1371/journal.pone.0068693.
[111] S. Bala, J. Petrasek, S. Mundkur, D. Catalano, I. Levin, J. Ward, H. Alao, K. Kodys, G. Szabo, Circulating microRNAs in exosomes indicate hepatocyte injury and inflammation in alcoholic, drug-induced, and inflammatory liver diseases, Hepatology 56 (5) (2012) 1946–1957, https://doi.org/10.1002/hep.25873.
[112] E. Rodriguez-Suarez, E. Gonzalez, C. Hughes, J. Conde-Vancells, A. Rudella, F. Royo, L. Palomo, F. Elortza, S.C. Lu, J.M. Mato, J.P. Vissers, J.M. Falcon-Perez, Quantitative proteomic analysis of hepatocyte-secreted extracellular vesicles reveals candidate markers for liver toxicity, J. Proteom. 103 (2014) 227–240, https://doi.org/10.1016/j.jprot.2014.04.008.
[113] Y.E. Cho, E.J. Im, P.G. Moon, E. Mezey, B.J. Song, M.C. Baek, Increased liver-specific proteins in circulating extracellular vesicles as potential biomarkers for drug- and alcohol-induced liver injury, PLoS One 12 (2) (2017) e0172463, https://doi.org/10.1371/journal.pone.0172463.
[114] M.O. Ogese, R.E. Jenkins, K. Adair, A. Tailor, X. Meng, L. Faulkner, B. O. Enyindah, A. Schofield, R. Diaz-Nieto, L. Ressel, G.L. Eagle, N.R. Kitteringham, C.E. Goldring, B.K. Park, D.J. Naisbitt, C. Betts, Exosomal transport of hepatocyte-derived drug-modified proteins to the immune system, Hepatology 70 (5) (2019) 1732–1749, https://doi.org/10.1002/hep.30701.
[115] J. Uetrecht, Mechanistic studies of idiosyncratic DILI: clinical implications, Front. Pharmacol. 10 (2019) 837, https://doi.org/10.3389/fphar.2019.00837.
[116] D. Dragoi, A. Benesic, G. Pichler, N.A. Kulak, H.S. Bartsch, A.L. Gerbes, Proteomics analysis of monocyte-derived hepatocyte-like cells identifies integrin beta 3 as a specific biomarker for drug-induced liver injury by diclofenac, Front. Pharmacol. 9 (2018) 699, https://doi.org/10.3389/fphar.2018.00699.
[117] N. van-Meteren, D. Lagadic-Gossmann, N. Podechard, D. Gobart, I. Gallais, M. Chevanne, A. Collin, A. Burel, A. Dupont, L. Rault, S. Chevance, F. Gauffre, E. Le Ferrec, O. Sergent, Extracellular vesicles released by polycyclic aromatic hydrocarbons-treated hepatocytes trigger oxidative stress in recipient hepatocytes by delivering iron, Free Radic. Biol. Med. 160 (2020) 246–262, https://doi.org/10.1016/j.freeradbiomed.2020.08.001.
[118] C. Yarana, D.K. St-Clair, Chemotherapy-induced tissue injury: an insight into the role of extracellular vesicles-mediated oxidative stress responses, Antioxidants 6 (4) (2017), https://doi.org/10.3390/antiox6040075.
[119] L. Palomo, J.E. Mleczko, M. Azkargorta, J. Conde-Vancells, E. Gonzalez, F. Elortza, F. Royo, J.M. Falcon-Perez, Abundance of cytochromes in hepatic extracellular vesicles is altered by drugs related with drug-induced liver injury, Hepatol. Commun. 2 (9) (2018) 1064–1079, https://doi.org/10.1002/hep4.1210.
[120] M. Li, Q. Luo, Y. Tao, X. Sun, C. Liu, Pharmacotherapies for drug-induced liver injury: a current literature review, Front. Pharmacol. 12 (2021) 806249, https://doi.org/10.3389/fphar.2021.806249.
[121] F. Jiang, H. Yan, L. Liang, J. Du, S. Jin, S. Yang, H. Wang, T. Hu, Y. Zhu, G. Wang, Y. Hu, T. Cai, G.P. Aithal, Incidence and risk factors of anti-tuberculosis drug induced liver injury (DILI): large cohort study involving 4652 Chinese adult tuberculosis patients, Liver Int 41 (7) (2021) 1565–1575, https://doi.org/10.1111/liv.14896.
[122] C. Sgro, F. Clinard, K. Ouazir, H. Chanay, C. Allard, C. Guilleminet, C. Lenoir, A. Lemoine, P. Hillon, Incidence of drug-induced hepatic injuries: a French population-based study, Hepatology 36 (2) (2002) 451–455, https://doi.org/10.1053/jhep.2002.34857.
[123] A. Suzuki, H.L. Tillmann, J. Williams, R.G. Hauser, J. Frund, M. Suzuki, F. Prior, G.P. Aithal, M.I. Lucena, R.J. Andrade, W. Tong, C.M. Hunt, Assessment of the frequency, phenotypes and outcomes of acute liver injury associated with amoxicillin/clavulanate in 1.4 million patients in the veterans health administration, Drug Saf. 46 (2) (2023) 129–143, https://doi.org/10.1007/s40264-022-01255-3.
[124] K. Wing, K. Bhaskaran, L. Pealing, A. Root, L. Smeeth, T.P. van Staa, O.H. Klungel, R.F. Reynolds, I. Douglas, Quantification of the risk of liver injury associated with flucloxacillin: a UK population-based cohort study, J. Antimicrob. Chemother. 72 (9) (2017) 2636–2646, https://doi.org/10.1093/jac/dkx183.
[125] A.K. Daly, P.T. Donaldson, P. Bhatnagar, Y. Shen, I. Pe'er, A. Floratos, M.J. Daly, D.B. Goldstein, S. John, M.R. Nelson, J. Graham, B.K. Park, J.F. Dillon, W. Bernal, H.J. Cordell, M. Pirmohamed, G.P. Aithal, C.P. Day, HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin, Nat. Genet. 41 (7) (2009) 816–819, https://doi.org/10.1038/ng.379.
[126] P. Nicoletti, G.P. Aithal, T.C. Chamberlain, S. Coulthard, M. Alshabeeb, J.I. Grove, R.J. Andrade, E. Bjornsson, J.F. Dillon, P. Hallberg, M.I. Lucena, A.H. Maitland-van der Zee, J.H. Martin, M. Molokhia, M. Pirmohamed, M. Wadelius, Y. Shen, M. R. Nelson, A.K. Daly, Drug-induced liver injury due to flucloxacillin: relevance of multiple human leukocyte antigen alleles, Clin. Pharmacol. Ther. 106 (1) (2019) 245–253, https://doi.org/10.1002/cpt.1375.
[127] S.P. Spielberg, G.B. Gordon, D.A. Blake, D.A. Goldstein, H.F. Herlong, Predisposition to phenytoin hepatotoxicity assessed in vitro, N. Engl. J. Med. 305 (13) (1981) 722–727, https://doi.org/10.1056/nejm198109243051302.
[128] M.A. Gennis, R. Vemuri, E.A. Burns, J.V. Hill, M.A. Miller, S.P. Spielberg, Familial occurrence of hypersensitivity to phenytoin, Am. J. Med. 91 (6) (1991) 631–634, https://doi.org/10.1016/0002-9343(91)90216-k.
[129] D. Larrey, A. Berson, F. Habersetzer, M. Tinel, A. Castot, G. Babany, P. Lettéron, E. Freneaux, J. Loeper, P. Dansette, Genetic predisposition to drug hepatotoxicity: role in hepatitis caused by amineptine, a tricyclic antidepressant, Hepatology 10 (2) (1989) 168–173, https://doi.org/10.1002/hep.1840100208.
[130] S. Hammond, P. Thomson, X. Meng, D. Naisbitt, In-vitro approaches to predict and study T-cell mediated hypersensitivity to drugs, 630530-630530, Front. Immunol. 12 (2021), https://doi.org/10.3389/fimmu.2021.630530.
[131] F. Hoentjen, S.B. Hanauer, N.K. de Boer, D.T. Rubin, Two brothers with skewed thiopurine metabolism in ulcerative colitis treated successfully with allopurinol and mercaptopurine dose reduction, Dig. Dis. Sci. 57 (1) (2012) 250–253, https://doi.org/10.1007/s10620-011-1999-x.
[132] A. Schosheim, D. Mockler, A. Chawla, Does genetics play a role in acute liver injury after amoxicillin exposure?, e00389-e00389, ACG Case Rep. J. 7 (6) (2020), https://doi.org/10.14309/crj.0000000000000389.
[133] A.K. Daly, Genetics of drug-induced liver injury: current knowledge and future prospects, Clin. Transl. Sci. 16 (1) (2023) 37–42, https://doi.org/10.1111/cts.13424.
[134] E.T. Cirulli, P. Nicoletti, K. Abramson, R.J. Andrade, E.S. Björnsson, N. P. Chalasani, R.J. Fontana, P. Hallberg, Y.J. Li, M.I. Lucena, N. Long, M. Molokhia, M.R. Nelson, J.A. Odin, M. Pirmohamed, T. Rafnar, J. Serrano, K. Stefánsson, A. Stolz, A.K. Daly, G.P. Aithal, P.B. Watkins, F. Bessone, I. Cascorbi, J.F. Dillon, C.P. Day, P. Hallberg, N. Hernandez, L. Ibanez, G. A. Kullak-Ublick, T. Laitinen, D. Larrey, A. Maitland-van der Zee, J.H. Martin, D. Menzies, S. Qin, M. Wadelius, A missense variant in PTPN22 is a risk factor for drug-induced liver injury, Gastroenterology 156 (6) (2019) 1707–1716, https://doi.org/10.1053/j.gastro.2019.01.034.
[135] P. Nicoletti, A. Dellinger, Y.J. Li, H. Barnhart, N.P. Chalasani, R.J. Fontana, J. A. Odin, J. Serrano, A. Stolz, A.S. Etheridge, F. Innocenti, O. Govaere, J.I. Grove, C. Stephens, G.P. Aithal, R.J. Andrade, E.S. Björnsson, A.K. Daly, M.I. Lucena, P. B. Watkins, Identification of reduced ERAP2 expression and a novel HLA allele as components of a risk score for susceptibility to liver injury due to amoxicillin-clavulanate, Gastroenterology 164 (3) (2023) 454–466, https://doi.org/10.1053/j.gastro.2022.11.036.

[136] P.S. Mitchell, R.K. Parkin, E.M. Kroh, B.R. Fritz, S.K. Wyman, E.L. Pogosova-Agadjanyan, A. Peterson, J. Noteboom, K.C. O'Briant, A. Allen, D.W. Lin, N. Urban, C.W. Drescher, B.S. Knudsen, D.L. Stirewalt, R. Gentleman, R. L. Vessella, P.S. Nelson, D.B. Martin, M. Tewari, Circulating microRNAs as stable blood-based markers for cancer detection, Proc. Natl. Acad. Sci. USA 105 (30) (2008) 10513–10518, https://doi.org/10.1073/pnas.0804549105.
[137] R.J. Church, G.A. Kullak-Ublick, J. Aubrecht, H.L. Bonkovsky, N.P. Chalasani, R. J. Fontana, J.C. Goepfert, F. Hackman, N.M.P. King, S. Kirby, P. Kirby, J. Marcinak, S. Ormarsdottir, S.J. Schomaker, I. Schuppe-Koistinen, F. Wolenski, N. Arber, M. Merz, J.M. Sauer, R.J. Andrade, F. van Bömmel, T. Poynard, P. B. Watkins, Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: an international collaborative effort, Hepatology 69 (2) (2019) 760–773, https://doi.org/10.1002/hep.29802.
[138] M. Chen, H. Bisgin, L. Tong, H. Hong, H. Fang, J. Borlak, W. Tong, Toward predictive models for drug-induced liver injury in humans: are we there yet? Biomark. Med. 8 (2) (2014) 201–213, https://doi.org/10.2217/bmm.13.146.
[139] T. Kralj, K.L.R. Brouwer, D.J. Creek, Analytical and omics-based advances in the study of drug-induced liver injury, Toxicol. Sci. 183 (1) (2021) 1–13, https://doi.org/10.1093/toxsci/kfab069.
[140] J. Concato, J. Corrigan-Curay, Real-world evidence: where are we now? N. Engl. J. Med. 386 (18) (2022) 1680–1682, https://doi.org/10.1056/NEJMp2200089.
[141] M. Kang, E. Ko, T.B. Mersha, A roadmap for multi-omics data integration using deep learning, Brief. Bioinforma. 23 (1) (2022) 1–16, https://doi.org/10.1093/bib/bbab454.
[142] A. Regev, M. Palmer, M. Avigan, L. Dimick-Santos, W.R. Treem, J.F. Marcinak, D. Seekins, G. Krishna, F.A. Anania, J.W. Freston, J.H. Lewis, A.J. Sanyal, N. P. Chalasani, Consensus Guidelines: Best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis, Aliment. Pharmacol. Ther. 49 (6) (2019) 702–713, https://doi.org/10.1111/apt.15153.
[143] G.P. Aithal, P.B. Watkins, R.J. Andrade, D. Larrey, M. Molokhia, H. Takikawa, C. M. Hunt, R.A. Wilke, M. Avigan, N. Kaplowitz, E. Bjornsson, A.K. Daly, Case definition and phenotype standardization in drug-induced liver injury, Clin. Pharmacol. Ther. 89 (6) (2011) 806–815, https://doi.org/10.1038/clpt.2011.58.
[144] H.J. Zimmerman, The spectrum of hepatotoxicity, Perspect. Biol. Med. 12 (1) (1968) 135–161, https://doi.org/10.1353/pbm.1968.0004.
[145] Food and Drug Administration (FDA), Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation, Drug Saf. (2009). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.
[146] M. Robles-Diaz, M.I. Lucena, N. Kaplowitz, C. Stephens, I. Medina-Caliz, A. Gonzalez-Jimenez, E. Ulzurrun, A.F. Gonzalez, M.C. Fernandez, M. Romero-Gomez, M. Jimenez-Perez, M. Bruguera, M. Prieto, F. Bessone, N. Hernandez, M. Arrese, R.J. Andrade, Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury, Gastroenterology 147 (1) (2014) 109–118, https://doi.org/10.1053/j.gastro.2014.03.050.
[147] P.H. Hayashi, D.C. Rockey, R.J. Fontana, H.L. Tillmann, N. Kaplowitz, H. Barnhart, J. Gu, N.P. Chalasani, R. Reddy, A.H. Sherker, J.H. Hoofnagle, Death and liver transplantation within 2 years of onset of drug-induced liver injury, Hepatology 66 (4) (2017) 1275–1285, https://doi.org/10.1002/hep.29283.
[148] M. Robles-Diaz, J. Sanabria-Cabrera, E.S. Björnsson, Therapeutic strategies for drug-induced liver injury: Review of the current literature, 1094732-1094732, Front. Pharmacol. 13 (2022), https://doi.org/10.3389/fphar.2022.1094732.
[149] H. Niu, J. Ma, I. Medina-Cáliz, M. Robles-Díaz, E. Bonilla-Toyos, M. Ghabril, M. I. Lucena, I. Álvarez-Álvarez, R.J. Andrade, Potential benefit and lack of serious risk from corticosteroids in drug-induced liver injury: An international, multicentre, propensity score-matched analysis, Aliment. Pharmacol. Ther. 57 (8) (2023) 886–896, https://doi.org/10.1111/apt.17373.
[150] M. Gromova, A. Vaggelas, G. Dallmann, D. Seimetz, Biomarkers: Opportunities and challenges for drug development in the current regulatory landscape, Biomark. Insights 15 (2020), https://doi.org/10.1177/1177271920974652.