

Organoids in the Clinic: A Systematic Review of Outcomes

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Organoids · Outcomes · Evidence · Systematic review

Abstract

Research on organoids has undergone significant advances during the last decade. However, outcomes from the use of organoids in clinical trials have not yet been documented. Therefore, there is an urgent need to assess the reporting of clinically relevant outcomes from organoid research in the scientific literature. This article presents a systematic review and appraisal of the published literature in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, together with a synopsis of recent relevant reviews. Surprisingly, no randomized controlled trials have reported clinical outcomes with any types of organoids. We found very few ongoing and registered studies that may provide clinically relevant results within this decade. Our screening and interpretation of the literature, including review articles, indicate a focus on technical and preclinical aspects of organoid research. This is the first systematic review of clinical trials involving organoids. Few clinical studies are planned or already underway, and, so far, no high-quality evidence relating to the clinical outcomes of or-

ganoid research has been published. The many promises of organoid research still need to be translated from bench to bed.

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Introduction

An organoid is usually defined as a three-dimensional biological structure that is grown in vitro from stem cells [Lancaster and Knoblich, 2014; Simian and Bissell, 2017]. The organoid, with its organ-specific cell types, takes on functional and structural (micro-anatomical characteristics) in vivo properties typical of live organs, albeit without resembling these organs' defined general architecture. Organoid research can be traced back to 1907 [Wilson, 1907]. Around 2010, research shifted from the development of two-dimensional (2D) to three-dimensional (3D) cultures [Corrò et al., 2020]. As indicated in Figure 1, organoid research has developed in two major waves.

The first wave of research is primarily characterized by reports focusing on various types of in vitro organ formation, such as breast epithelia [Li et al., 1987], “artificial

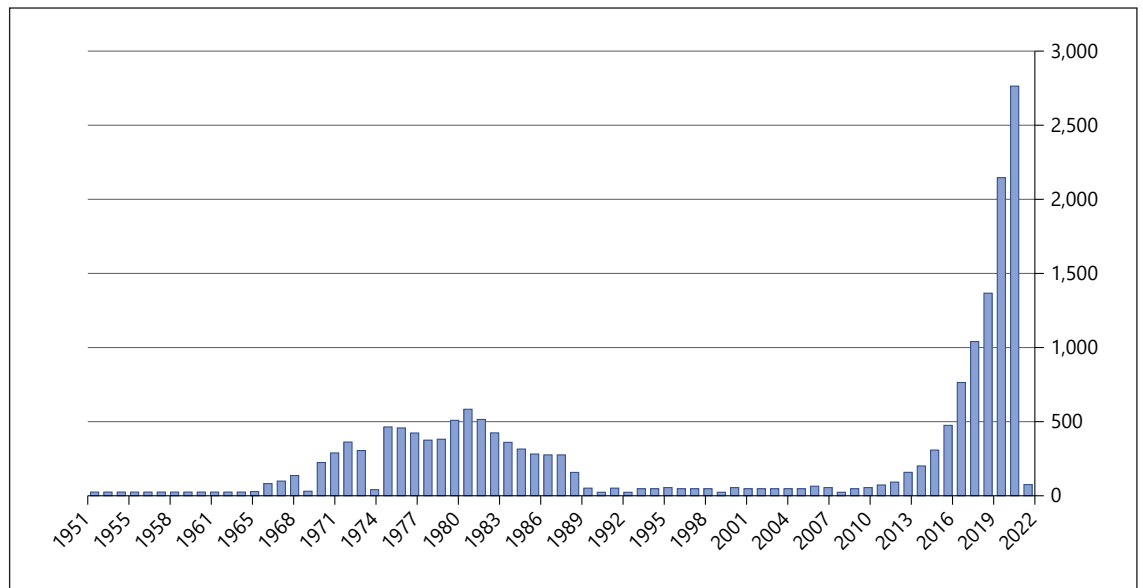


Fig. 1. Number of publications on organoids registered in MEDLINE (PubMed) per year from 1950 to 2021.

thyroids” [Martin et al., 1999], “lung organoids” [Zimmermann, 1987], and various types of cancer-derived organoids [Doetschman et al., 1985]. The second wave has seen researchers derive organoids from stem cells [Corrò et al., 2020]. Pluripotent stem cells such as human embryonic stem cells and induced pluripotent stem cells can demonstrably develop into any type of human organoid and, thereby, in principle, imitate any type of tissue or organ of the human body. Organoids can also be derived from tissue-resident multipotent adult stem cells. As part of this second wave of organoid research, organoids have been used to model pathologies of human genetic and congenital disorders and specific diseases, including Alzheimer’s disease, fronto-temporal dementia, cystic fibrosis and the Zika virus infection [Ming et al., 2016; Saini, 2016; Xu et al., 2016; Bartfeld and Clevers, 2017; Bredenoord et al., 2017; Chen et al., 2019b, 2021; Bowles et al., 2021].

Many researchers anticipate that organoid-based modeling of human pathologies will lead to clinical translation, particularly in the contexts of precision and personalized medicine. For example, organoids might (a) serve as new standards for personalized models of specific diseases, (b) be used in preclinical testing of certain therapies, (c) aid better understanding of human drug metabolism, (d) be used to develop standardized, pharmacy-ready drugs, and (e) facilitate personalized treatment regimens in general [Dekkers et al., 2016; Ming et

al., 2016; Xu et al., 2016; Berkers et al., 2019; Chen et al., 2019b; Lensink et al., 2021].

In the field of regenerative medicine, the strategy of transplanting organoids to repair or replace damaged tissues or even whole organs builds on scientific principles governing stem-cell-based treatments. These treatments have been tested in human clinical trials for stroke, traumatic brain injury, and Parkinson’s disease [Chen et al., 2019a]. However, where such applications are concerned, research on organoids is faced with certain limitations regarding their complexity and maturity when compared with real organs, including the challenges of oxygen and nutrient diffusion, the absence of a peripheral nervous system, and the associated problems of modeling different parts of an organ in an *in vivo* environment [Chen et al., 2019a].

Despite much high-intensity research, and although applications in precision, personalized, and regenerative medicine are widely foreseen [Bartfeld and Clevers, 2017; Bredenoord et al., 2017; Chen et al., 2019b], the trials on which such applications would be based are still in the preclinical phase. In addition, as this study will demonstrate through a systematic review of the literature, no clinical outcomes have been demonstrated or reported in randomized control trials. As described by the Cochrane collaboration, “empty reviews” are of great value as they can not only identify knowledge gaps and direct research efforts [Yaffe et al., 2012] but also point to challenges with traditional modes of knowledge production.

With this study, we assessed the current state of organoid research with respect to clinical translation. We identified some of the challenges currently facing the clinical application of organoid technologies. We also attempted to gauge whether current anticipations of clinically relevant outcomes are a matter of overextended expectations or principled “hype” [Simian and Bissell, 2017; Mead and Karp, 2019], rather than empirically grounded promises.

Materials and Methods

In this work, we systematically searched for published research that applied organoids in randomized controlled clinical trials and that reported clinically relevant outcomes.

Criteria for Selection of Relevant Studies

We defined criteria for selection of relevant primary studies as shown in Table 1. For relevant literature reviews, we did not use objective criteria but discussed and selected a number of studies that seemed relevant summaries of recent research on organoids upon reading the title and abstract.

Literature Search

Academic librarian Hilde Strømme, at the Library of Medicine and Science, University of Oslo, developed the search strategies together with Bjørn Hofmann and performed all searches on July 13, 2021. Upon request during the review of our manuscript, senior librarian Toril M. Hestnes updated and performed new searches on June 30, 2022. For details on our literature search strategies and results, see online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000527237) (including PRISMA 2020 checklist).

We searched the following databases:

- MEDLINE (Ovid)
- Embase (Ovid)
- Cochrane Database of Systematic Reviews (Wiley)
- Epistemonikos
- Scopus (Elsevier)

We also searched the following registers:

- Cochrane Central Register of Controlled Trials (Wiley)
- ClinicalTrials.gov

We searched for reports of organoids derived from any organ or tissue (e.g., tumor, liver, heart, kidney, brain, ovaries, etc.) or synonyms thereof. We tailored our searches to systematic reviews, health technology assessments, and randomized controlled trials (RCTs) of human participants (i.e., not experimental animal models), including registered, ongoing, and planned clinical trials. We imported all references to Endnote [Clarivate, 2020] and eliminated duplicate records (see Fig. 2, 3).

Selection of Relevant Studies

We transferred all references to Covidence [Veritas Health Innovation, 2009] and selected studies that met our predefined criteria. The software automatically identified and excluded additional duplicate records.

Each reference was screened by two researchers (B.H., S.Z., S.H., J.L., or P.K.) independently of one another. Each researcher

Table 1. Inclusion and exclusion criteria for study selection

	Criteria for inclusion	Criteria for exclusion
Population	Human participants in clinical trials regardless of age, gender, medical condition, or other biological or socioeconomic parameters	
Intervention	Any type of organoid except bone or cartilage tissue	Organoids derived from bone or cartilage tissue, as these organoids are not usually derived from stem cells
Comparison	Any comparison such as placebo or any other control	Studies without a control group
Outcome	Any clinically relevant outcome, e.g., efficacy, effectiveness, or clinical benefit	Studies that reported only safety, side effects or adverse events, cost-benefit calculations, or economic models
Study design	Planned, ongoing, discontinued, and completed randomized controlled trials	Non-randomized trials and studies that did not report results from human patients
Publication type	Original research articles as well as planned and ongoing studies published in scientific journals and clinical trial registers	
Language		Articles published in languages we were unable to translate

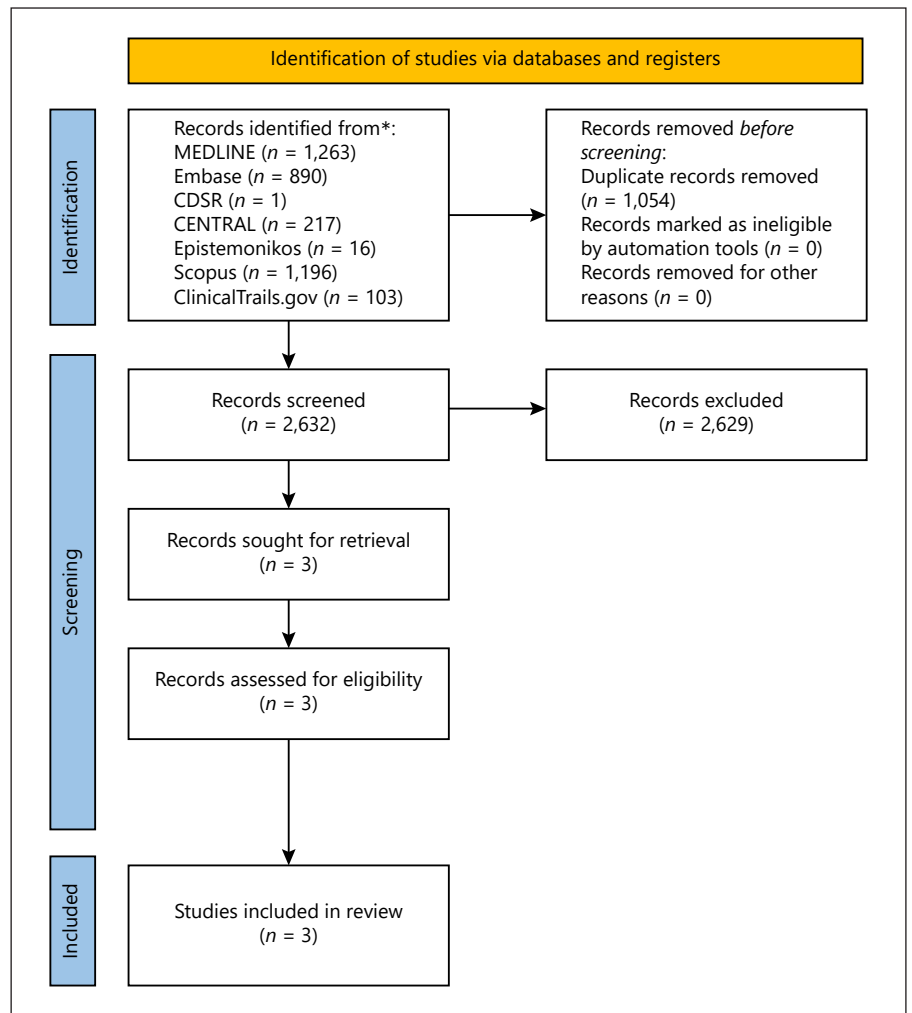


Fig. 2. PRISMA flow chart [Page et al., 2021].

read the title and abstract and decided whether to include or exclude the study based on the criteria presented in Table 1. Conflicting decisions were resolved by a third researcher (B.H. or S.Z.), who re-evaluated the title and abstract and made a final decision.

We had planned to evaluate any included studies for further and final inclusion or exclusion based on full-text publication of study results. However, as we identified no studies that met our criteria based on title and abstract, this task was superfluous.

Risk of Bias and Certainty of Results

We had planned to evaluate the risk of bias of any included studies and outcomes using the Cochrane risk-of-bias tool 2.0 [Higgins et al., 2022]. We also planned to assess the certainty of the evidence (i.e., our confidence in the reported results) by GRADE [Schüneman et al., 2013]. As we identified no RCT that met our criteria, these tasks were superfluous.

Data Extraction

We had planned to extract relevant data from any included RCT. As we identified no RCT that met our criteria, this task was superfluous.

We selected systematic or narrative review studies that we identified through our searches and deemed informative for the scope of this health technology assessment. One researcher (B.H., S.Z., S.H., J.L., or P.K.) extracted the following data from each review article based on a defined set of parameters:

- First author
- Title
- Publication year
- Journal where the review was published
- Type of organoid or organoids reviewed
- Characteristics or focus of the review
- Criteria, endpoints, and outcomes assessed
- Current stage of the reviewed research
- Promises or hopes reported

Two researchers (B.H., S.Z.) reviewed and made final decisions on all extracted data.

Other Assessments

A full health technology assessment was planned, but as no high-quality studies were included, the economic, ethical, and social implications of organoids in clinical practice could not be assessed.

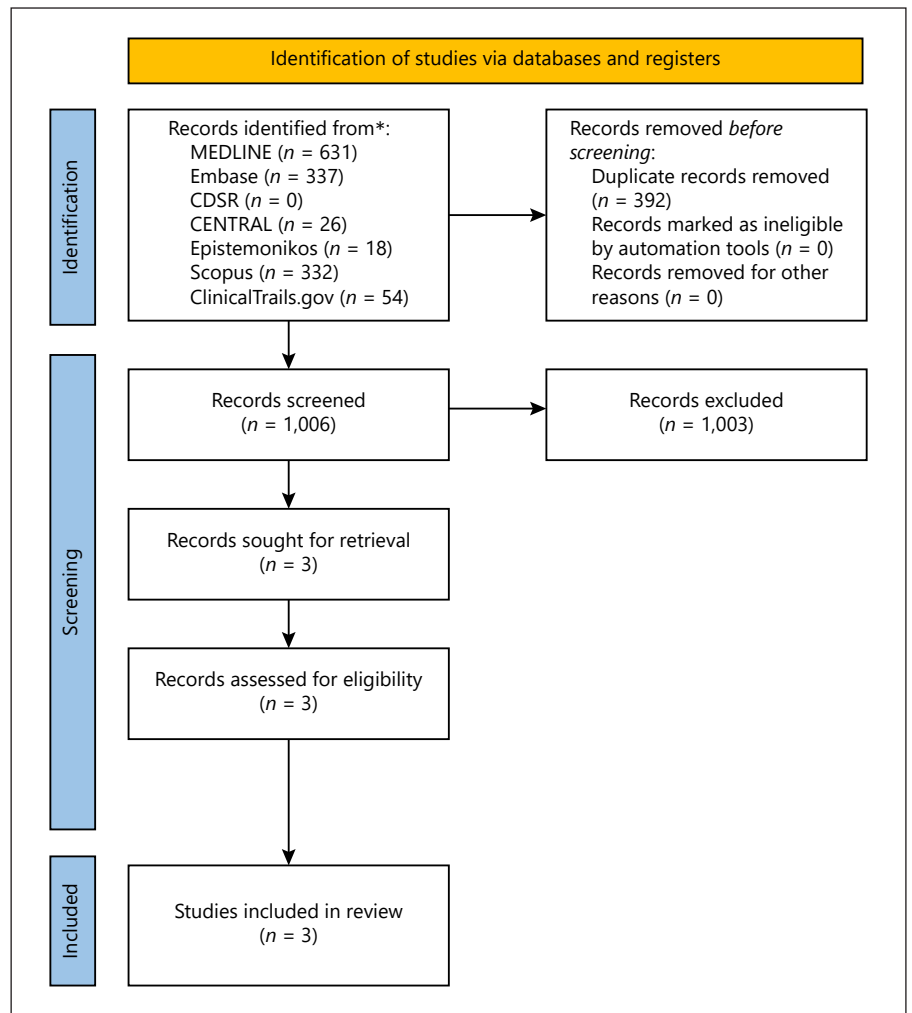


Fig. 3. PRISMA flow chart [Page et al., 2021].

Results

We searched for any systematic reviews and health technology assessments as well as planned, ongoing, and completed RCTs of human organoids on July 13, 2021. We were requested to update our searches upon review of our manuscript and performed these on June 30, 2022. Figures 2 and 3 show flow charts of the literature searches performed and the results from screening the retrieved literature. For details on our literature search strategies, see online supplementary material.

Randomized Controlled Trials Reporting Clinical Outcomes

We found no published RCT that met our criteria (Table 1) and that reported measured clinical outcomes of organoid research. However, such studies may be pub-

lished in the future as there are RCTs that are currently ongoing or registered and that plan to report clinical outcomes.

Planned and Ongoing Randomized Controlled Trials

Currently, several trials (see Fig. 2, 3; Table 2) plan to test the use of organoid technologies for choice of therapy in patients with cancer [University Health Network, 2020; ShiWei, 2021; Seppälä, 2021; Lau, 2022; Sun, 2022]. These six trials plan to recruit between 93 and 200 patients, and their results may be expected within 2–10 years (see Table 2). We also found a recent review [Chen et al., 2021] that mentioned two “high-profile” RCTs being underway in China, but we were unable to retrieve those studies.

Table 2. Overview of ongoing randomized controlled studies with clinical outcomes from using organoids

Principal investigator	Title	Type of organoid	Design	Status	Planned completion	Patients needed
Elizabeth Jaffee, Baltimore, USA and Jennifer J Knox, Toronto, Canada	Pancreatic Adenocarcinoma Signature Stratification for Treatment (PASS-01) [University Health Network, 2020]	Pancreatic cancer	Randomized Parallel Controlled Open Label	Recruiting	September 2023	150
James Yun-Wong Lau, Hong Kong	Patient-derived-organoid (PDO) Guided versus Conventional Therapy for Advanced Inoperable Abdominal Tumors [Lau, 2022]	Metastatic or inoperable solid abdominal tumors	Randomized Parallel Controlled Open Label	Not yet recruiting	July 2025	140
Jing Sun, Shanghai, China	The Clinical Efficacy of Drug Sensitive Neoadjuvant Chemotherapy Based on Organoid versus Traditional Neoadjuvant Chemotherapy in Advanced Rectal Cancer [Sun, 2022]	Rectal cancer	Randomized Parallel Controlled Open Label	Not yet recruiting	December 2025	192
Toni T. Seppälä, Helsinki, Finland	Systemic Neoadjuvant and Adjuvant Control by Precision Medicine in Rectal Cancer (SYNCOPE) [Seppälä, 2021]	Rectal cancer	Randomized Parallel Controlled Open Label	Recruiting	December 2031	93
Gang Jin, Shanghai, China	Organoid-Guided Chemotherapy for Advanced Pancreatic Cancer [ShiWei, 2021]	Pancreatic cancer	Randomized Parallel Controlled Open Label	Recruiting	N/S	100
Gang Jin, Shanghai, China	Organoid-Guided Adjuvant Chemotherapy for Advanced Pancreatic Cancer [ShiWei, 2021]	Pancreatic cancer	Randomized Parallel Controlled Open Label	Recruiting	N/S	200
N/S, not stated.						

Discussion

In the field of organoid research, efforts are currently underway to use these not only for scientific investigation but to develop them for clinical application. For example, therapeutic decisions can be made based on the results of testing treatment alternatives on patient-derived organoids (PDO) *ex vivo* prior to clinical intervention (see also Further Research, below). In one such recently registered study [Lau, 2022], patients will receive either standard treatment without or treatment guided by a drug screen using organoids derived from their own tumor tissue in a randomized fashion. Another possible application in the clinic would be to replace damaged tissue with a live, three-dimensional organoid structure, for instance, the transplantation of stem cell-derived islet-like organoids in patients with type 1 diabetes [de Klerk and Hebrok, 2021].

Despite the extensive history of organoid research, we were unable to identify results on clinically relevant outcomes reported from high-quality studies. Although ongoing or registered clinical trials involving organoids indicate that clinical results may be available in the future, there is currently a gap between the expectations expressed by researchers in the review literature – concerning the clinical applications of organoids and organoid technologies – and the current state of organoid research. There may well be reasons that support these expectations, but the lack of evidence from high-quality clinical studies suggests that if such justification is available, then it is likely to be based on principled considerations, including those that draw on preclinical testing and animal modeling.

The Current State of Clinically Relevant Organoid Research from Reviews

As there are few RCTs for clinical outcomes on the way, the systematic reviews identified by our search may provide some overview of ongoing and published studies and detail the clinical prospects of organoid research, as they offer updated summaries of past and currently ongoing organoid research. For example, four publications present results on cancer organoids [Ishiguro et al., 2017; Aberle et al., 2018; Medle et al., 2022; Sisman et al., 2022], seven on organoids derived from healthy tissue [Alves-Lopes and Stukenborg, 2018; Nugraha et al., 2018; De Miguel et al., 2019; Aasen and Vergara, 2020; Schneemann et al., 2020; Shrestha et al., 2020; Samimi et al., 2021], and one discusses the potential of organoids in general to imitate extracellular vesicles [Abdollahi, 2021].

The types of cancer organoids studied are glioma, breast, colon, ovary, prostate, bladder, and gastrointestinal organoids [Ishiguro et al., 2017; Aberle et al., 2018; Medle et al., 2022; Sisman et al., 2022]. Types of healthy organoids include heart, testis, liver, lung, retinal, and thyroid organoids [Alves-Lopes and Stukenborg, 2018; Nugraha et al., 2018; De Miguel et al., 2019; Aasen and Vergara, 2020; Schneemann et al., 2020; Shrestha et al., 2020; Samimi et al., 2021]. Eight of the ten publications are narrative reviews [Ishiguro et al., 2017; Aberle et al., 2018; Alves-Lopes and Stukenborg, 2018; Nugraha et al., 2018; De Miguel et al., 2019; Aasen and Vergara, 2020; Shrestha et al., 2020; Abdollahi, 2021], one is a systematic review [Samimi et al., 2021], and one is a policy article [Schneemann et al., 2020].

All retrieved reviews report that the results are either at an experimental or at a preclinical stage, without any clinical applications at this point in time. Specifically, the two publications on cancer organoids [Ishiguro et al., 2017; Aberle et al., 2018] detail experimental and preclinical results that have the potential for clinical applications. Two reviews on healthy organoids explicitly state that the results are at a preclinical stage, namely, heart organoids for *in vitro* modeling and drug testing [Nugraha et al., 2018] and liver organoids for transplantation [Schneemann et al., 2020]. In terms of the remaining six publications related to healthy organoids, research is, currently, at the experimental stage. Specifically, these reviews cover: (a) testis organoids and their use for *in vitro* modeling of testicular architecture, physiology, and functionality [Alves-Lopes and Stukenborg, 2018]; (b) liver organoids for disease modeling, and for transplantation in animals [De Miguel et al., 2019]; (c) retinal organoids for modeling of retinal pathology from patient-derived cells [Aasen and Vergara, 2020]; (d) lung-on-a-chip devices for the study of lung physiology models, toxicity testing models, etiology models, and testing of pharmacological agents [Shrestha et al., 2020]; (e) thyroid organoids for understanding morphological, histological, and physiological characteristics of the thyroid gland and tissue reconstruction [Samimi et al., 2021]; and (f) organoids that simulate extracellular vesicles for cancer, cardiac repair, and stem cell studies [Abdollahi, 2021].

In terms of the expectations regarding the clinical application of organoid research, several reviews explicitly refer to the potential for clinical implementation in terms of precision, personalized, or regenerative medicine [Aberle et al., 2018; Aasen and Vergara, 2020; Schneemann et al., 2020; Shrestha et al., 2020; Medle et al., 2022; Sisman et al., 2022]. Others, in relation to specific clinical applica-

Table 3. Overview of reviews on organoid research (our emphasis in quotations to ease reading)

Study	Title	Journal	Type of organoid	Type of study	Characteristics	Assessment criteria/endpoints/outcomes	Stage of research	Promise or hype
Ishiguro et al. [2017]	Tumor-derived spheroids: Relevance to cancer stem cells and clinical applications	Cancer Science	Cancer stem cells: glioma, breast, colon, ovary, and prostate cancer spheroids	Narrative review	3D; organotypic multicellular tumor spheroids; tumor-derived organoids; tumor-derived spheroids	<ul style="list-style-type: none"> In vivo tumorigenicity or chemoresistance Self-renewal Capable of differentiation Expression of specific cancer stem cell markers Capable of spheroid formation 	Mainly experimental No clinical or near clinical outcomes	" likely to be of clinical importance"
Nugraha et al. [2018]	Modeling human cardiac diseases with 3D organoid	European Heart Journal	Heart	Narrative review	3D; human-like tissues; pluripotent stem cell-derived cardiomyocytes; cardiac organoids	<ul style="list-style-type: none"> Creating human iPSC lines with specific mutations Repair known gene mutations by CRISPR editing, reversing diseased cells to normal function Regeneration capacity of cardiac organoids 	Preclinical in vitro modeling and drug testing	"organoid models [that] closely resemble human tissues [have] brought significant advancement in the development [...] of novel and innovative therapies" "the careful development of human cardiac organoids will speed up [...] drug discovery and personalized cardiac treatment"
Aberle et al. [2018]	Patient-derived organoid models help define personalized management of gastrointestinal cancer	British Journal of Surgery	Gastrointestinal cancer	Narrative review with non-systematic literature search	PDOs; patient-specific organoid model; 3D "mini-organs"; organoid-like 3D cell cultures	<ul style="list-style-type: none"> Molecularly guided personalized treatment in cancer therapy Molecular testing of disease Biomarker analysis Drug sensitivity assays "Omic" analysis, gene-expression profiling Standard immunohistochemical arrays Pharmacotyping 		" potential for implementation in clinical practice as a guide for precision medicine", "patient-specific avatars of disease" "organoid development [has] made preclinical modeling of individual patient tumors a viable strategy in personalized medicine" "the efficiency of the personal organoid model allows immediate clinical implementation" "The design of adaptive clinical trials, with a treatment arm allocation according to tumor phenotype and organoid pharmacotype, may be more promising and attractive for both patients and clinicians than traditional RCTs with current treatment standards." " could rapidly transform the field of cancer therapeutics"
Alves-Lopes and Stukenborg [2018]	Testicular organoids: a new model to study the testicular microenvironment in vitro	Human Reproduction Update	Testis	Narrative review with non-systematic literature search	Testicular organoids; testicular- and seminiferous-like structures	Infertility; subfertility; spermatogenesis; spermatogonial stem cell differentiation, proliferation, niche regulation; in vitro organization	In vitro model testicular architecture, physiology and functionality	"Testicular organoids might provide a new and promising variation on already existing methods" "human testicular organoids [...], might also represent a platform to test the safety and efficiency of future in vivo genetic therapies"
De Miguel et al. [2019]	Mesenchymal stem cells for liver liver failure: From experimental models to clinical trials	Stem Cells International	Mesenchymal stem cells (MSC); liver	Narrative review	Stem cells; adipose-derived MSC; bone marrow-derived MSC; endothelial cells; organoid; in vivo generation of liver organoid; hepatobiliary organoid; hepatic organoid	Treat hepatic lesions; liver regeneration	<ul style="list-style-type: none"> Experimental MSC studies show increase proliferation of hepatocytes. Both in vitro and in vivo Animal models for cirrhosis treatment using MSC Clinical trials with MSC for liver failure (mainly cirrhosis) Most organoid studies focus on the development of liver organoids for liver disease modeling Organoid transplantation in animals 	<p>"MSC therapy promising for reducing and preventing liver fibrosis and disease", "end-stage cholestatic liver disease"</p> <p>"Several animal models for both acute and chronic cirrhosis and liver fibrosis treatment with MSC have shown benefits" "More research needed before establishing MSC therapy as a treatment for liver failure" "Not enough data to compare organoid with MSC treatment"</p>

Table 3 (continued)

Study	Title	Journal	Type of organoid	Type of study	Characteristics	Assessment criteria/endpoints/outcomes	Stage of research	Promise or type
Shrestha et al. [2020]	Lung-on-a-chip: the future of respiratory disease models and pharmacological studies	Critical Reviews in Biotechnology	Lung	Narrative review	Lung-on-a-chip; multicellular 3D cultures; microfluidic biosystems; microfabricated biosystems; modeling	<ul style="list-style-type: none"> Crucial to identify physiological hallmarks for individual organs and define universal standards for design, fabrication, and utility Before preclinical modeling, microfluidic models require further improvements to reproduce physiological mechanisms Before modeling inheritable respiratory diseases and conducting drug studies, need to find a way to generate lung-specific cells from iPSC 	<ul style="list-style-type: none"> Lung-on-a-chip device techniques: <ul style="list-style-type: none"> Lithography based microfabrication Thermoplastic technique 3D Cell bioprinting Lung-on-a-chip studies developed lung physiology models, toxicity testing models and disease etiology models Experimental studies testing pharmacological agents 	<p>"Widely anticipated that organ-on-chip models will be utilized in toxicity testing, reducing need for animal studies, and in the study of pathophysiological mechanisms of different lung diseases"</p> <p>"Great potential to facilitate development of drugs for respiratory disorders"</p> <p>Potential for lung-on-a-chip models to develop cells for the production of personalized chips</p> <p>Possibility of using stem cells within lung-on-a-chip for lung repair"</p>
Schneemann et al. [2020]	Ethical challenges for pediatric liver organoid transplantation	Science Translational Medicine	Liver	Policy article	Children in first-in-human clinical trials; research ethics; clinical trials regulations	<ul style="list-style-type: none"> Before first pediatric clinical trials begin, risks, uncertainties, burdens, efficacy, and benefits of liver organoid transplantation should be determined through preclinical animal models Preclinical evidence must consist of proof of concept in an animal model of metabolic liver disease showing liver organoid engraftment and >5% liver function recovery First-in-human liver organoid trial should be a combined safety and efficacy study 	<ul style="list-style-type: none"> Proof of concept for liver organoid transplantation has been demonstrated in animal models Current research is still in preclinical stages, and clinical safety and efficacy have yet to be established for liver organoid transplantation Human hepatocyte transplantation has shown potential clinical benefit 	<p>"pediatric liver may provide more favorable microenvironment for engraftment of liver organoids"</p> <p>"Potential individual benefits of liver organoid transplantation can be expected"</p> <p>"Human fetal and adult mature hepatocytes might be safer alternatives to adult human liver progenitor cells for producing liver organoids"</p>
Aasen and Vergara [2020]	New Drug Discovery Paradigms for Retinal Diseases: A Focus on Retinal Organoids	Journal of Ocular Pharmacology & Therapeutics	Retinal	Narrative review	Human iPSC-derived organoid models; incorporation of organoid technologies in standard drug development pipeline; organoid-on-a-chip; microfluidic biosystems	<ul style="list-style-type: none"> Augmentation of existing drug development pipeline with retinal organoids, rather than replacement of existing pathway components 3D organoid systems as an intermediate step between 2D cultures and animal models in a secondary screening and validation phase, reducing animal experimentation without need to meet initial screening quantities necessary for the first steps of drug screening 	<ul style="list-style-type: none"> Retinal organoids have achieved advanced levels of cellular maturation, including the ability to respond to light Organoid studies have displayed some success in modeling retinal pathology from patient-derived cells Organoid technology is not mature enough to meet the high-throughput demands of the first stages of drug screening 	<p>"Human iPSC-derived organoid technology has the potential to realize the promise of personalized medicine and decrease the likelihood of rejection in transplantation approaches"</p> <p>"Today's drug development pathways are not sufficient, and organoids developed from human iPSCs might be tomorrow's answer"</p> <p>"iPSC-derived organoids hold significant promise for improving upon the current drug development process"</p> <p>"Microfluidic chips representing multiple organs to evaluate efficacy, toxicity and side effects represent an ambitious prospective avenue for development"</p>
Samimi et al. [2021]	A systematic review on thyroid organoid models: time-trend and its achievements	American Journal of Physiology – Endocrinology & Metabolism	Thyroid	Systematic review	3D functional thyroid follicles and organoids for thyroid research	<ul style="list-style-type: none"> Organoid technology and its potential applications in understanding morphological, histological, and physiological characteristics of the thyroid gland and reconstructing this tissue Use of organoids to investigate the tumorigenesis process of thyroid 	<p>Only a few studies exist related to the organoid technology and its potential applications in understanding morphological, histological, and physiological characteristics of the thyroid gland and reconstructing this tissue</p> <p>No study exists using organoids to investigate the tumorigenesis process of thyroid</p>	<p>"The exciting and promising organoid technology offers researchers:</p> <ul style="list-style-type: none"> A wide range of potential applications for more accurate modeling of thyroid in health and diseases An excellent preclinical in vitro platform." <p>"In the future, organoid technology can provide a better understanding of the molecular mechanisms of pathogenesis and tumorigenesis of thyroid tissue and more effective treatment for related disorders due to more accurate simulation of the thyroid physiology."</p>
Abdollahi [2021]	Extracellular vesicles from organoids and 3D culture systems	Biotechnology and Bioengineering	Not defined	Narrative review	Organoids and other multicellular 3D in vitro systems that could imitate extracellular vesicles (EV)	<ul style="list-style-type: none"> Progress using 3D in vitro culture models for EV analysis Organoids and other multicellular 3D in vitro systems to understand the implications of cell-cell contact on EV ultimately, commercialization covering EV from organoids and 3D in vitro culture systems and contributes to understanding the progress in the field and standardizing techniques 	<ul style="list-style-type: none"> Therapeutics are at different stages of clinical trials, and the EV are derived from a variety of sources such as MSC and even plants EV with 3D in vitro models are mainly studied in the contexts of cancer, cardiac repair, and stem cells 	<p>Initiation of human clinical trials for EV therapeutics, including intravenous administration, which may extend to EV from 3D in vitro systems</p>

2D, two-dimensional; 3D, three-dimensional; EV, extracellular vesicles; iPSC, induced pluripotent stem cell; MSC, mesenchymal stem cells.

tions, claim that they are “likely” [Ishiguro et al., 2017], that they “might” occur [Alves-Lopes and Stukenborg, 2018], or that they are “promising” [De Miguel et al., 2019]. Still others seem to be more confident in their expectations. For instance, Samimi et al. [2021] claim that “in [the] future, organoid technology can provide [...] more effective treatment for related disorders.” By contrast, Nugraha et al. [2018] make no explicit claims regarding the likelihood of the clinical translation of organoid research but, instead, state that the development of organoids “will speed up” drug development and personalized treatment processes. In terms of those that expressed their expectations, there seem to be two ways of explaining their lack of certainty. First, and as already mentioned, all of the identified reviews make explicit that much of the research under discussion is at an experimental or preclinical stage. Second, most of the review articles also discuss the key technical, methodological, ethical, or regulatory challenges facing organoid technologies in terms of their translation from the bench to the clinic. Table 3 provides an overview of the systematic reviews discussed here.

While our results are limited with respect to clinical outcomes, our short discussion on the reviews identified in our search provides some insights into the current state of organoid research. In particular, the majority of the reviews posit precision, personalized, or regenerative medicine applications as assessment criteria, endpoints, or outcomes. Where organoid research is concerned, researchers have reported and described how they have derived organoids of different stages of complexity and maturation and modeled physiology, functionality, and pathology of organs or organ parts in vitro.

In addition, preclinical modeling of toxicity tests, including the use of animals, disease etiology models, and drug tests using organoids, organ-on-a-chip, or organoids in combination with other types of stem cells, have also been reported. Finally, results concerning certain types of organoid transplantation in animal models have been reported as well.

According to the research discussed in the review literature, key challenges facing organoid technologies for clinical translation are (a) improved organoid complexity and maturation; (b) improved preclinical modeling of therapeutics and specific organ physiology, functionality, and pathology; (c) preclinical establishment of efficacy, benefits, risks, uncertainties, and burdens in animal models; (d) assessment of whether current clinical trial protocols and drug development pathways are suitable for the testing of specific organoid technologies; and (e) defining universal standards for the design, fabrication, and utility

of organoids. This information makes it possible to assess whether current expectations regarding the clinical relevance and application of organoids are based on scientific findings or whether the expectations are a reflection of the hype surrounding organoid research [Huch et al., 2017; Little, 2017; Simian and Bissell, 2017; Xinaris, 2019].

Promise or Hype?

Although current organoid research is characterized by great enthusiasm and is perceived to be promising for clinical application [Huch et al., 2017], the expectations for the clinical translation of organoids and organoid technologies expressed by researchers in the identified reviews seem to be indicative of hype (derived from principled considerations) rather than statements that can be empirically grounded on directly applicable (i.e., in-human) clinical studies. Developments in organoid research seem to, at this point in time, coincide with the so-called peak of inflated expectations on Gartner’s hype cycle [Fenn and Raskino, 2008]. The lack of high-quality clinical trials in the field indicates that more research is needed to reach “the plateau of productivity.”

While there are reasons to be optimistic about the future outcomes from present organoid research, we ought to take lessons from its history [Corrò et al., 2020] and question whether organoid research is hyped [Huch et al., 2017; Little, 2017; Simian and Bissell, 2017; Marsoner et al., 2018; Xinaris, 2019]. At present, more convincing scientific knowledge and discussion of the clinical usefulness of organoids are warranted. This is especially true in relation to the direct application of organoids for therapeutic purposes, where the path from what works in the laboratory to well-evidenced, routine clinical use is highly complex.

We do not wish to suggest that the absence of results on clinically relevant outcomes reported from high-quality studies calls into question the potential or widely acknowledged suitability of organoids and organoid technologies for clinical purposes. First, as we have already suggested, there seem to be principled reasons that support the expectations being expressed by researchers in this area. Second, given that stem-cell-derived organoids are a new product of bioengineering, and, indeed, the use of induced pluripotent stem cells for organoid derivation is even more innovative, it seems reasonable to claim that the current absence of clinically relevant outcomes is to be expected when we take into account the development processes and dynamics from the bench to the clinic. But clinically verified outcomes of high quality must be made available over time to maintain the belief in the field.

New Modes of Knowledge Production

Organoids may even complicate the usual processes by which new therapeutics make their way into clinical practice. For instance, many kinds of organoid research belong to a type of personalized medicine, where traditional modes of evidence production are inadequate or challenged by the nature and extension of the research. Organizing RCTs may become difficult, resource demanding, time consuming, and legally and ethically challenging. In such contexts, alternative study designs may be needed [Lillie et al., 2011; Gronowicz, 2016].

In addition, organoid research highlights Collingridge's dilemma [Collingridge, 1982], according to which, on the one hand, we cannot properly assess a technology before it is extensively developed and widely used ("the information problem"), while, on the other hand, it is difficult to control or regulate its use when the technology is widely used ("the power problem"). Hence, if one were to assess a novel technology too early, one might miss important innovations, while assessing it too late makes the assessment irrelevant (as one is effectively powerless to prevent its use) [Genus and Stirling, 2018].

Although our criteria for clinical outcomes were wide, they may still be too strict to identify all clinically interesting outcomes. Additionally, there are many small non-randomized studies demonstrating various effects of organoids. By July 13, 2022, 54 clinical trials were registered at ClinicalTrials.gov. For example, PDOs have been employed to predict treatment outcome of cystic fibrosis patients [Kim et al., 2020].

Further Research

While it may be disappointing that this systematic review of the literature did not identify high-quality evidence of clinical outcomes from RCTs, our findings are relevant for future research for four reasons. First, our method and findings can be used in future systematic reviews and meta-analyses, and, as a result, similar studies need not search or screen the literature before 2022. Second, the lack of outcomes from organoid research, despite substantial research in the 1970s and 1980s and again in the last 14 years, indicates a need for reflection on organoid evidence production. Does all the research on organoids result in improved patient management and better health? Third, "empty reviews" are acknowledged as important for evidence production [Yaffe et al., 2012] in identifying knowledge gaps and directing further research funding. There are many examples of "empty reviews" [Martí-Carvajal et al., 2011; Gaskell et al., 2016; Amorim et al., 2017], and 8.7% of the reviews in the Co-

chrane Database of Systematic Reviews have been reported to be empty [Yaffe et al., 2012]. Fourth, as pointed out in a recent review on PDOs as a predictive biomarker for treatment response in cancer patients, "ultimately, the clinical value of using PDO individualized tumor response testing should be proven by comparing clinical outcomes, such as progression-free survival or response rates, in randomized clinical trials comparing physician-guided standard of care treatment versus assay-guided treatment derived from PDO drug screens" [Wensink et al., 2021]. Moreover, graphical presentation of existing research may make knowledge gaps even more visible [Ding et al., 2022].

Conclusion

We provide the first systematic review of clinical trials from organoid research. We found no high-quality clinical outcomes from RCTs involving organoids. Consequently, it is difficult to provide a proper health technology assessment for organoid technologies (including their economic, ethical, legal, and social implications). Some ongoing studies indicate that clinical outcomes can be expected in the next 10 years. However, our screening of the literature and identified reviews show that the majority of research has investigated technical and preclinical aspects of organoids. While both enthusiasm and expectations in this field are high, research still seems to be situated at "the peak of inflated expectations," according to Gartner's hype cycle. It will be crucial to assess technologies emerging from organoid research early. Despite many years of organoid research, our study may still have come too early, but we argue that its results may well be relevant for similar assessments of organoids in the future.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Bjørn Hofmann and Severin Zinöcker designed the study. Severin Zinöcker and Bjørn Hofmann assisted in the design of the literature searches. Bjørn Hofmann, Severin Zinöcker, Jonathan Lewis, Søren Holm, and Panagiotis Kavouras participated in the screening, evaluation, and selection of research studies, contributed to the writing and revision of the manuscript, and have approved the final version of the manuscript. Bjørn Hofmann drafted the first version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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