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| **Abstract:** | We propose hereby a new topic group for the "Artificial Intelligence for Health" project. The topic group will focus on the identification and diagnosis of infertility as well as treatment associated steps of Assisted Reproductive Technologies with the applications of artificial intelligence and machine learning. It is estimated that 9% of the global population of reproductive age is infertile [1]. While infertility affects one in six couples in the U.S. [2], in developing countries it is estimated that one in four couples face reproductive difficulties [3]. Applications of AI and technology have the potential to improve patient identification, diagnosis, and treatment journey for patients in need of IVF treatment worldwide.  |

Attachment:

* Presentation of the proposal
<https://extranet.itu.int/sites/itu-t/focusgroups/ai4h/docs/FGAI4H-L-034-A01.pdf>

# Overview

We propose to create a topic group to focus on early identification, diagnosis and treatment decision support of infertility related conditions with the applications of artificial intelligence (AI) and machine learning (ML) and other approaches.

**Patient identification:** Infertility is currently characterised by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner. [4]. Even though this definition can serve as guidance, the earliest infertility can be identified and treated, and live birth of a healthy baby achieved, the better. There are two main reasons driving the urgency in initiating treatment early as possible: (i) the psychological burden on patients going through infertility [5] and (ii) the facts that gamete quality decreases ageing [6,7].

The application of technologies that can assist in theearly identification of patients that are still not aware of being at risk of need of fertility treatment in the short-midterm future is of extreme importance. The use of AI and ML could effectively support the identification of any infertility risk by analysing existing electronic health records (EHR) of patients that underwent fertility treatment (including data from wearables with the patients’ consent) compared to healthy population.

**Diagnosis:** Infertility is a highly complex disorder of the reproductive system. There are 2 forms of male or female sterility: primary and secondary. The primary form affects germ cell structure or physiology, causing arrest of germ cell development and ultimately cell death. Primary female infertility includes premature ovarian failure (POF), polycystic ovary syndrome (PCOS), endometriosis, and leiomyoma. Primary male sterility disrupts spermatogenesis and is associated with abnormal semen (i.e., abnormal sperm count, morphology, or motility), but often the semen is normal (idiopathic infertility). Secondary infertility arises due to systemic or syndromic genetic defects, including developmental, endocrine, and metabolic defects [8]Therefore, the identification of a specific cause/disease can take months and sometimes years to be correctly identified and therefore treated efficiently. The use of AI could assist in identifying at higher efficiency the main conditions that can lead to reproductive challenges. This more efficient diagnosis could take place at the clinical practice by combining demographical, lifestyle and genetic data. In addition, the capturing of a patient’s signs and symptoms including pain, irregular menstrual cycles and others biological indicators could also be supported using chatbots and similar approaches to reduce time of diagnosis.

**Treatment:** The fertility treatment is complex as it combines several activities managed by several healthcare professionals, such as obstetrician-gynaecologists, nurses, andrologists and embryologists. There are today several types of treatments and techniques that vary in level of complexity and invasiveness depending on the patient diagnosis [9]. In addition, differently from other treatments, a part of the treatment of infertility happens extracorporeally while gametes and embryo are handled in in vitro conditions until the transfer back to the patient/receptor uterus.

Differently from other therapeutic areas, Human Reproduction treatments are relatively new, and this field has been witnessing intense progress over the past 40 years [10]. Consequently, there are several possible treatments, strategies and techniques when stimulating patients, selecting gametes and embryos as well as supporting early stage of pregnancy. The use of AI in fertility treatment can be applied to support clinicians in decision making processes during the selection of treatment regimens and protocols, the definition of medication starting dosage as well as the continuous adjustment during stimulation protocol and the decision of ideal time for triggering of ovulation. In the laboratory setting, AI can be used as support tool to define the techniques to be used for each patient and to select the best embryo for transfer back to patient.

We suggest using topic group names interchangeably depending on context: “AI for fertility treatment” and “AI for infertility treatment”, “ART treatment” and “Fertility treatment”.

# Relevance

Infertility is more than a quality-of-life issues, with considerable public health consequences including psychological distress, social stigmatization, economic strain, and marital discord. Globally, infertility affects 15% of couples at reproductive age [11]. In addition, infertility has also been associated with an increased risk of subsequent chronic health conditions such as cardiovascular disease [12].

The infertility stigma is no longer associated to females exclusively. It is estimated that out of ~50 million couples suffering from the condition, 1/3 is attributed to female factors, 1/3 attributed to male factors and 1/3 classified as unexplained or a combination of both partners. This makes fertility unique to other clinical conditions, as it does not only rely in one individual, but a couple and their biological interaction [13].

Large amounts of data are generated as part of ART treatments. This is due to the biological complexity and variability of root causes that can lead to infertility. Moreover, the stepwise and complex nature of the laboratory procedures and add-on techniques that aim to improve treatment outcomes contribute to the data generation. The selection of the right treatment, gamete and embryo selection as well as times of procedures are within the areas that could benefit the most from AI applications that could support the clinical decision-making process.

There have been few developments in the last few years that are particularly relevant for this area, but most of them still in early stage of development:

* The development of tools that support the selection of blastocyst with highest potential of implantation and live birth
* The development of support software that assists the clinician during ovarian stimulation in the decision of dosage adjustment and ovulation triggering
* The development of wearables that track biomarkers such as core basal temperature to predict ovulation and diagnosis of high incidence infertility related conditions

# Impact

Artificial intelligence has the potential to enable more affordable, accessible, and accurate diagnostics, prevention, and care for people across the world who are either at risk of developing or who have existing infertility.

The use of AI for infertility could provide rapid access to information of being at risk of requiring ART treatment. It could also facilitate the work of clinicians, for example by supporting diagnosis and treatment guidance. The impact of such solutions is therefore spread across the full journey of infertile patients.

Recent and rapid progress of AI applications to infertility has highlighted the potential positive impact for fertility treatment, but also the importance and the need of guidelines for development and validation. It is therefore vital to develop and maintain a set of diversified and robust benchmarks to ensure accurate, safe, scalable solutions that are applicable at different stages for different patient groups.

# Existing Work

In recent years, the number of companies and academic groups focusing on this area has sharply increased. While most of the AI applications have a strong focus on laboratory related activities, few groups have focused on personalized treatments protocols or individualized transfers [14]. As exciting opportunities and innovation are spreading into this field, Merck hosted the First International Fertility Artificial Intelligence Forum in Lisbon on 21st-22nd November 2019 with the participation of 25 experts from 9 countries (Australia, Canada, Czech Republic, Denmark, Korea, Spain, Portugal, USA, UK). During the event, a multi-disciplinary team consisting of doctors, embryologists, engineers, data scientists, health tech companies and business partners had the possibility to discuss and exchange on current developments and challenges in fertility. After discussing recent studies and applications of AI in protocol stimulation, gamete viability assessment and embryo implantation potential, two workstream groups were identified to deeper brainstorm on quality standard, guidance and best practise in AI development and applications. A white paper focusing on the requirements to proper develop robust algorithms, ensuring transparency and clinical value, was published in the Journal of Assisted Reproduction and Genetics on September 2020 by the Fertility AI Forum group [15]. A follow-up online meeting has been held in 2020 to connect, update and plan a new Fertility AI Forum in 2021.

The potential and the benefits that AI could bring into this field are tremendous. However, challenges and limitations have been already identified and a collaborative and multi-disciplinary approach could be a key asset to build the foundation of robust and reliable development and validation of applications.

# Feasibility

We believe the work that this topic group is proposing is feasible and much needed.

The work of the topic group could be guided by the following directions:

1. Looking for new topic group members and facilitating the collaboration between existing topic group members. We currently have a list of multidisciplinary key opinion leaders that would be interested in being part of this group.
2. Assessing the fertility treatment landscape and defining areas of focus.
3. Scoping the existing and emerging applications of AI for Human Reproduction and Fertility.
4. Creating and supporting of guidelines for reliable and interpretable AI applications in Human Reproduction and Fertility.
5. Facilitating the aggregation, publication, processing of data for training and testing.
6. Creating benchmarks (including prototypes and guidelines) and supporting the benchmarking process.

# 6-9 Data Availability, Data Quality, Annotation/label quality, Data Provenance

To the best of our knowledge, there is generally no publicly available data for the training or testing of AI for Human Reproduction and Fertility.

However, there is non-publicly available data held by different entities including public and private medical bodies, academic and research institutions, and private companies. The generation and collection of data in ART is therefore fragmented. Many different ecosystems are currently being used in clinics worldwide for data generation, collection, and storage. Various equipment and technologies are used during fertility treatment and different Electronic Medical Records (EMRs) systems have been implemented according to clinic needs and therefore different information and parameters are captured using different format and units. In addition, given the small general population of infertile patients seeking treatment compared to other therapeutic areas, the available data size might be a limiting factor. A harmonization approach would therefore be beneficial to successfully address current challenges of data availability, facilitating the integration of different data sets and the exchange across clinics. Furthermore, the definition of data standard and data quality would facilitate the pre-processing and the modelling of data collected from different data sources and consequently reduce the complexity of the steps that are necessary to properly validate the robustness of the developed solutions.

One of the functions of the topic group could be to facilitate the collection, publication, and processing of data. Any data activities (from collection to modelling to benchmarking) requires an environment fulfilling regulatory requirements to guarantee safety, reliability, and transparency. The data quality and the data sample size are often key elements for an AI application development. Labels and clinical outcomes are the most important data aspects for supervised models, and therefore they need to be properly collected or assessed. Additionally, robustness of an algorithm depends on the variability of the data and particularly on how representative is the data used for development of the population under study for the specific problem. Any bias or constraints present in the collected data need to be evaluated and corresponding measures to be taken for potential correction.

# Benchmarking

The table below shows the possible applications of the AI for Human Reproduction and Fertility. The details of the potential applications are reported.

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| **Application** | **Type of Data** | **Details** |
| Patient Identification | Data on general population (patients and control group): demographics, behaviours and lifestyle, medical history (including all relevant fertility treatment data) | Early identification of potential patients based on infertility indicators and behavioural attributes  |
| Consultation | Data on demographics, behaviours and lifestyle, medical history, prior fertility treatments with clinical outcomes | Predicting likelihood of success for a new patient or a new treatment cycle |
| Stimulation and Triggering | Data on patients including demographics, medical history, treatment protocols with any clinical evaluation (e.g., hormone levels) and clinical outcomes  | Support personalized treatment protocols to increase treatment success  |
| ART Lab  | Data on patients including demographics and medical history, data on cycles, on gamete and embryo development (e.g., videos of embryo development, annotations) and clinical outcomes | Support any decision in the lab to select the most viable gametes and embryos  |
| Transfer and Pregnancy | Data on patients including demographics and medical history, data on cycles with any clinical evaluation (specific to this stage) and clinical outcomes | Predicting receptivity of the endometrium for a successful outcome (optimal transfer and pregnancy) |

# Other applications might be identified and studied as part of this topic group.

The benchmark of the above applications could require slightly different specifications. However, it is important to underline that clinical outcomes need to be considered as ground truth for any application development and validation. In case of comparison with human annotations, it is necessary to compare with several experts to assess and evaluate expert variability. Performances of any developed algorithm must be reported with quantifiable metrics and must be measured on hold-out data, a subset of data that is not used to train and test a model, but only for validation. Analyses can be developed on retrospective data, but a prospective validation is additionally required to verify the robustness and reliability of the application.

# Organiser

Merck, a leading science and technology company, operates across healthcare, life science and electronics. Around 58,000 employees work to make a positive difference to millions of people’s lives every day by creating more joyful and sustainable ways to live: from advancing gene editing technologies and discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices.

Merck in Fertility - Merck has a strong heritage of over 60 years of fertility expertise and is the world’s innovative market leader in fertility treatments. Through pioneering science and technology Merck develops and provides innovative therapeutics, digital health solutions, lab technologies and services to help people realize their dreams of parenthood, at every stage of their fertility journey. To date, more than four million babies have been born with the support of Merck’s fertility treatments [16].

Susanna Brandi is Head of Portfolio Expansion at Merck KGaA. Susanna is a biomedical scientist with a Master’s in Human Reproduction at Università Degli Studi di Napoli Federico Secondo. Susanna worked as an embryologist at the Genea IVF Group in Sydney, Australia. She migrated to product development within the company focusing on automation and standardization of techniques and process within the IVF Laboratory. Susanna has been working with Merck for four years co-leading the assessment of AI and digital health associated products.

Eleonora Lippolis is Senior Data Scientist at Merck KGaA. Eleonora holds a Master’s degree in Bioengineering from the University of Pavia and a degree in Science and Technologies from the Italian Institute of Advanced Studies of Pavia. She worked as research assistant at the Institute of Human Genetics in Erlangen, Germany. She joined Merck four years ago and since has successfully led several data science healthcare projects.

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