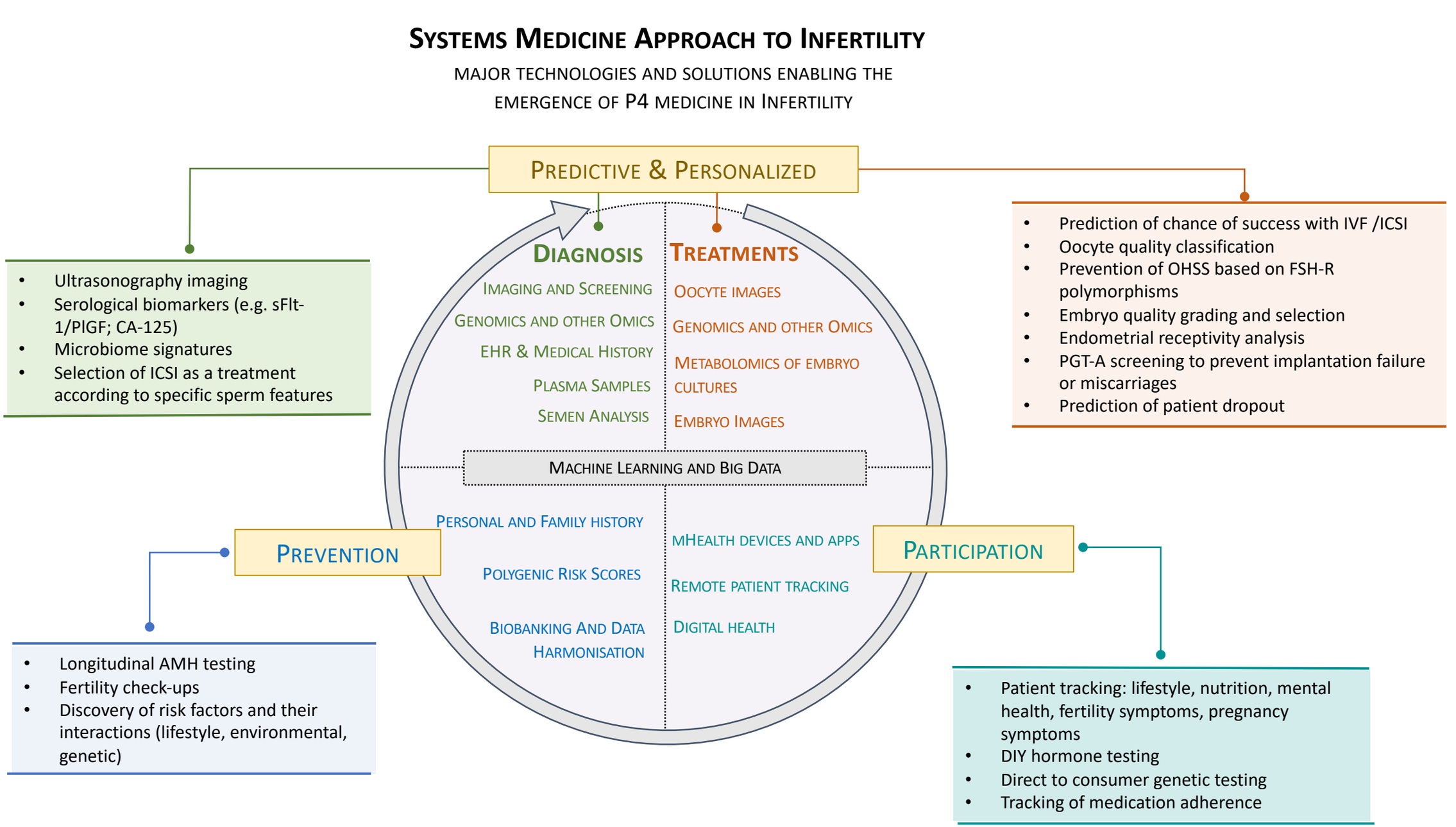


Figure 1: The systems approach to infertility. The figure shows the major technologies and solutions enabling the emergence of a P4 system in infertility. 'Prevention' refers to the ability to prevent infertility disorders or pregnancy complications. 'Predictive and Personalized' refer to the prediction and management of disease with greater granularity and the individualization of treatments. 'Participation' refers to patient participation in their own health. The text inside the circle indicates key data sources generated by each segment that can be integrated using ML and Big data mining techniques. Text boxes outside the circles include practical examples of the use of these data sources. At the centre of the circle we highlight 'Machine Learning and Big Data', which are essential to every of the four sections to power the innovation cycle of a 'systems medicine approach' to Infertility.

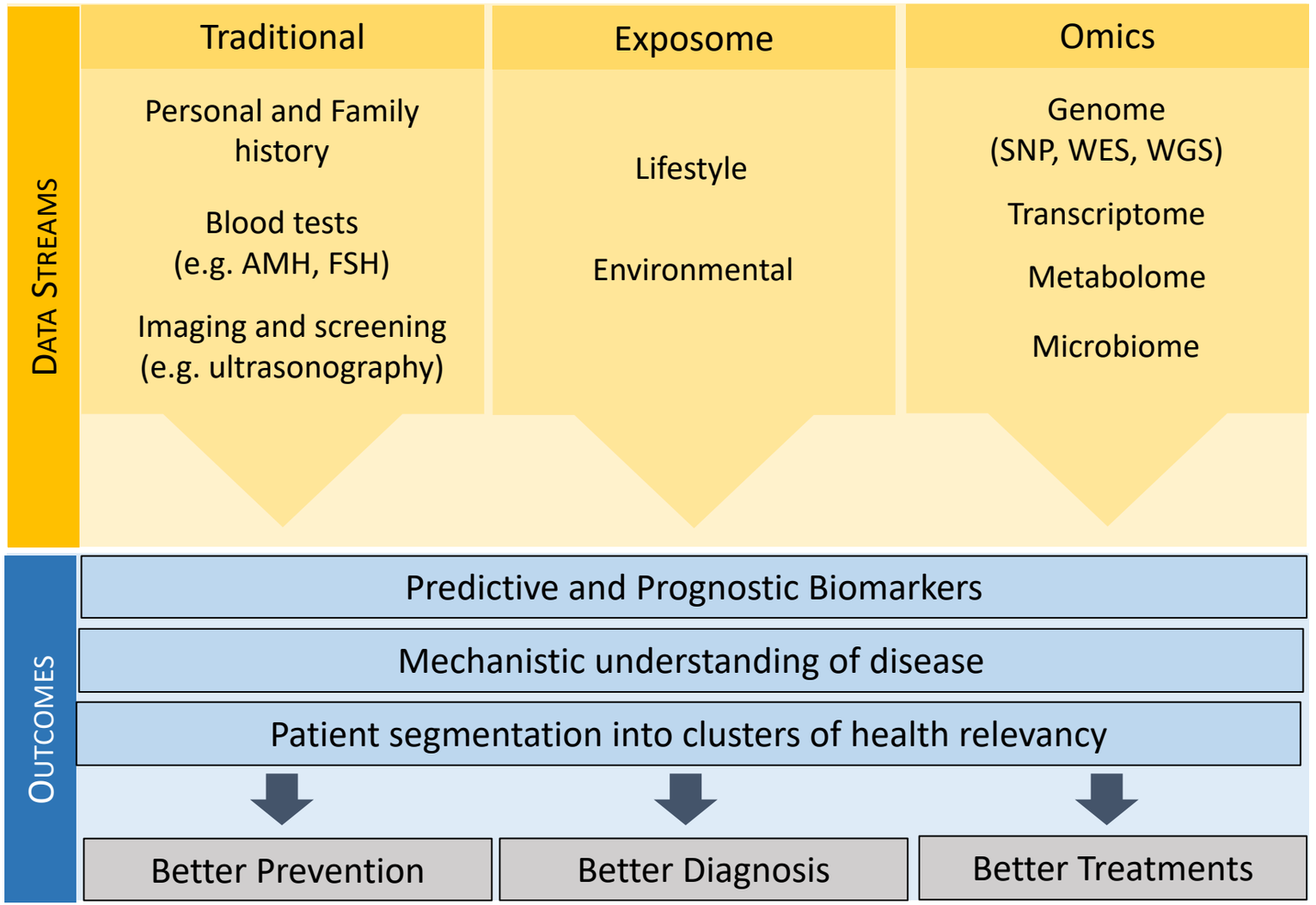


Figure 2: Data streams used to enable precision medicine in the Infertility sector. The newer health data streams such as genomics, the microbiome and the exposome are a complement to traditional approaches used in infertility investigations and management, to ultimately deliver better prevention, diagnosis and treatments.

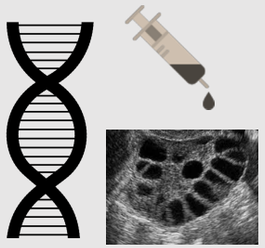
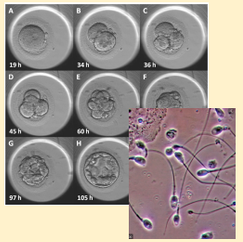
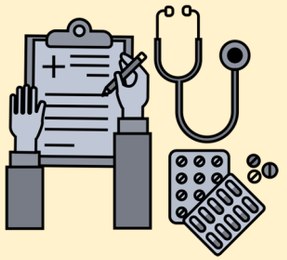
Examples of input data	 • Genotypes (e.g. CYP2D6, FSH-R, STK11) • Biomarkers of ovarian reserve (e.g. AMH, AFC)	 • Embryo Images (e.g. time-lapse) • Oocyte images • Sperm analysis	 • Ultrasound images of the endometrium • Molecular receptivity data	 • Baseline characteristics (e.g. BMI, comorbidities) • Infertility history • IVF treatment data (e.g. number eggs retrieved) • Previous pregnancies and duration	 • Biomarkers of pregnancy (e.g. beta-hCG, PAPP-A, fetal fibronectin) • Clinical history (e.g. any cervical surgery?) • 2D or 3D ultrasonographic images • Fetal nuchal fold thickness
Examples of ML/AI applications	**Ovulation Stimulation** • Individualization of ovarian stimulation protocols. • Choosing among GnRH-agonists or antagonists for FSH suppression. • Choosing the correct FSH starting dose.	**Fertilization** • Selection of the most appropriate treatment (IVF or ICSI). • Selection of oocytes for fertilization. • Prediction of embryo viability.	**Embryo transplantation** • Selection of best timing for embryo transfer. • Prediction of chances of viable pregnancy.	**IVF treatment outcomes** • Appropriate counselling regarding chance of success per treatment cycle started. • Appropriate counselling regarding any additional treatments such as novel and unproven add-ons. • Guide on how many cycles that may be required. • Better financial planning for patients. • Prediction of patient dropout.	**Pregnancy care** • Prediction of risk of miscarriage and preterm delivery. • Accurate non-invasive assessment of fetal chromosomal anomalies.

Figure 3: Examples of different types of input data and ML models that can be built and applied to improving ART treatments.

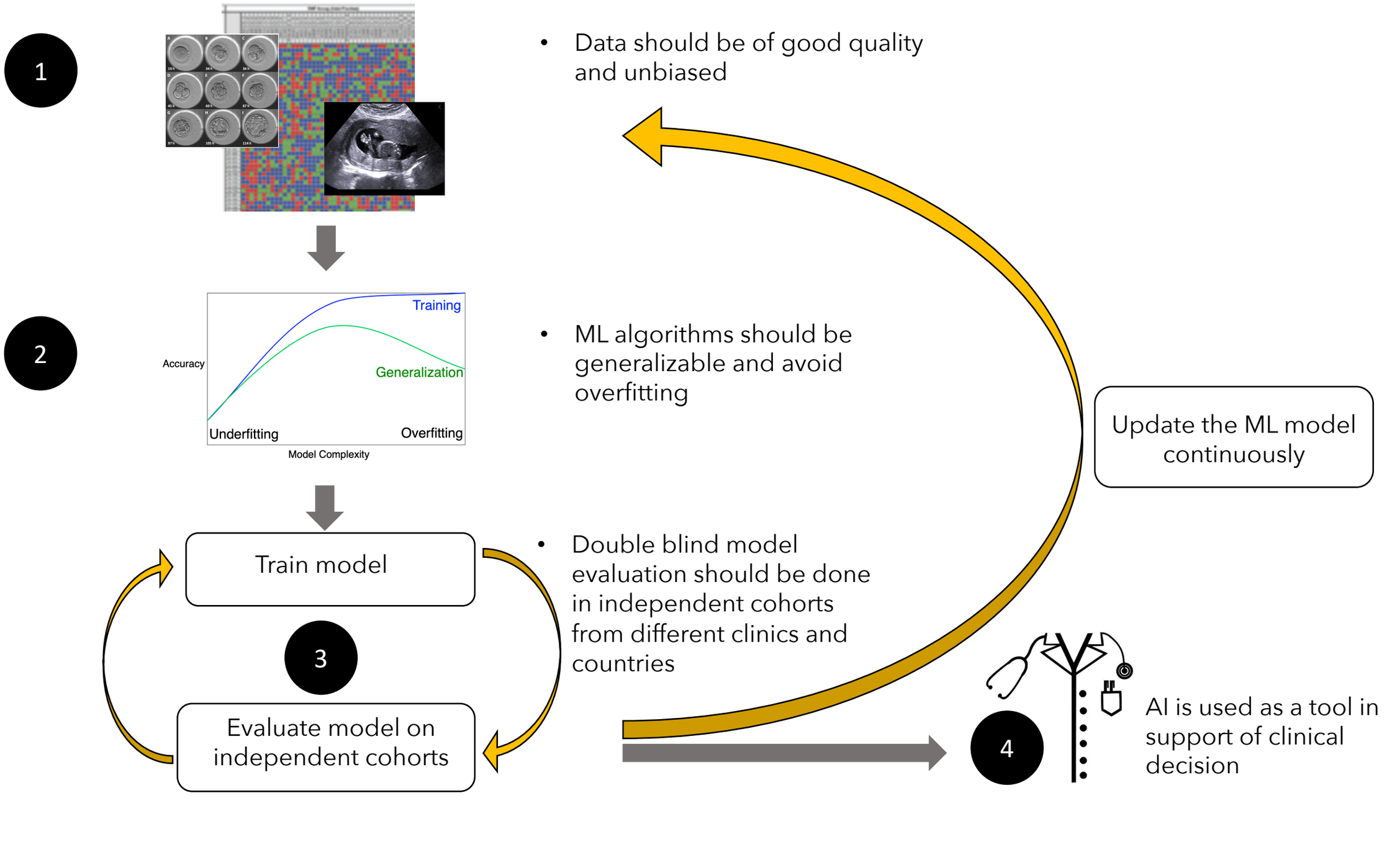


Figure 4: Challenges associated to the use of ML/AI algorithms. (1) Data should be labelled accurately and unbiased; (2) ML/AI algorithms should be generalisable and avoid overfitting; (3) Algorithms should be validated in independent cohorts and continuously updated; (4) Algorithms need to be translated and adopted into clinical practice.