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   Sommario/riassunto Virtual reality (VR) and augmented reality (AR) have long histories in the healthcare sector, offering the opportunity to develop a wide range of tools and applications aimed at improving the quality of care and efficiency of services for professionals and patients alike. The best-known examples of VR–AR applications in the healthcare domain include surgical planning and medical training by means of simulation technologies. Techniques used in surgical simulation have also been applied to cognitive and motor rehabilitation, pain management, and patient and professional education. Serious games are ones in which the main goal is not entertainment, but a crucial purpose, ranging from the acquisition of knowledge to interactive training.These games are attracting growing attention in healthcare because of their several benefits: motivation, interactivity, adaptation to user competence level, flexibility in time, repeatability, and continuous feedback. Recently, healthcare has also become one of the biggest adopters of mixed reality (MR), which merges real and virtual content to generate novel environments, where physical and digital objects not only coexist, but are also capable of interacting with each other in real time, encompassing both VR and AR applications.This Special Issue aims to gather and publish original scientific contributions exploring opportunities and addressing challenges in both the theoretical and