For improving quality and safety of healthcare as well as efficiency and efficacy of care processes, health systems turn toward personalized, preventive, predictive, participative precision medicine (5P Medicine). The resulting ecosystem combines different domains represented by a huge variety of different human and non-human actors belonging to different policy domains, coming from different disciplines and so deploying different methodologies, terminologies, and ontologies. They offer different levels of knowledge, skills, and experiences, act in different scenarios and accommodate different business cases for meeting the intended business objectives. In that context, currently practiced data level interoperability has to advance to dynamic and individually tailored knowledge-based cooperation. For correctly modeling and managing such systems and their behavior, a system-oriented, architecture-centric, ontology-based, policy-driven approach, standardized in ISO DIS 23903 Interoperability and Integration Reference Architecture, is inevitable. Requirements and solutions for designing and implementing advanced 5P Medicine ecosystems with reference to related standards, specifications and projects will be discussed in necessary detail.