Typical comparative genomics analyses consider either single-copy genes across multiple species, or multi-copy genes between pairs of species. Multi-copy genes across multi-species remains hard. Yet genomes are replete with multi-copy genes. In my talk I will describe a framework to overcome this issue, and show in the context of several published and unpublished applications how this can be used to integrate knowledge across different species to elucidate gene function and reconstruct biological networks.