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Customized Medicine for Corals

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EDITORIAL—CORAL REEF RESEARCH SECTION

Coral reefs are facing unprecedented pressures, on a global scale. Alarming declines in coral abundance and diversity are occurring across the majority of reef systems, driven by the cumulative impacts of local stressors and rapidly changing climate (Hughes et al., 2017, 2018). Increases in the greenhouse gas emission (GGE) rates are linked with marine heatwaves which cause mass coral bleaching events, a phenomenon reported as the main threat to coral reefs into the future (Sweet and Brown, 2016). The recent global coral bleaching event from 2014 to 2017 resulted in extensive mortality impacting reef functioning in ways not previously recorded (Eakin et al., 2019). The knock-on effects of this global environmental extreme are still playing out with recent assessment on the Great Barrier Reef (GBR) demonstrating drastic declines in coral recruitment, which may fundamentally change the ecosystem dynamics across this region into the future (Hughes et al., 2019). In addition, regional stressors such as overfishing, poor water quality, and pollution can also severely affect the health state of corals and reefs (Shaver et al., 2018). Most agree that the reduction of GGE rates is the priority to ensure the persistence of coral reef ecosystems, however under current GGE projections, annual mass coral bleaching events are expected to occur as early as 2050 (National Academies of Science, Engineering and National Academies of Sciences, 2018). Even if GGE emissions are significantly reduced, further decline of reef health appears unavoidable due to the current accumulation of greenhouse gases in the atmosphere and the predicted lag period before any change will be observed (Hoegh-Guldberg et al., 2007; National Academies of Sciences, 2018). This poses a major problem to those caring for and managing reef ecosystems.

Coral bleaching events can be assessed through satellite monitoring of sea surface temperatures, however no effective mitigation strategies to lessen the impacts of bleaching on coral populations are currently available (National Academies of Sciences, 2018). While reducing GGE should be our focus, there is also an urgent need to move away from simply documenting the demise of coral reefs and explore options that can assist corals and build their resilience to the increasing number of threats they face. This is no trivial task and complicated further by the stochasticity of the environment across different regions with unique biotic and abiotic characteristics, including different cumulative impacts and threat levels posed. There is certainly no "magic recipe," which can be applied on a global scale to reverse the declines in coral reef ecosystem health. However, the same principles that are applied to, and have improved human health, are relevant to the management of corals at the individual, population and ecosystem levels.

EXPLORING THE "CUSTOMIZED MEDICINE" APPROACH

All organisms differ in their genotype and phenotype, with each individual's genetics, epigenetics, and associated microbiome critical to overall health status. In humans for example, each person contains a diverse set of traits that can make them either resilient or vulnerable to diseases and,

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at the same time, influence their response to specific treatments. For this reason, a new array of personalized approaches, aimed at improving a given individuals health has emerged, where genetics, epigenetics and multi-omics surveys inform the health status of the individual and their response to specific treatments (Schüssler-Fiorenza et al., 2019; Steinhubl, 2019). Importantly, while the approach relies on the comprehensive risk assessment at an individual level and the ability of detecting pre-clinical signs of unbalance (dysbiosis), it can also be hugely beneficial through the development and application of individual preventive approaches to avoid poor health outcomes in the first place (Schüssler-Fiorenza et al., 2019). Adapting the same concepts of personalized medicine (considering medicine in the broader sense of any compound, treatment, management, or application to remedy decline) to build resilience of corals through customized interventions at the species (populations), or community (reef scale) level should be a priority and opens up new areas for research. Such approaches are undoubtedly going to be challenging for corals (and reefs more broadly) and will certainly rely on a multipronged strategy.

The first of this multipronged approach should always be aimed at "prevention" and this should stay the priority objective, i.e., removing the factors that contribute to poor or reduced health state and, in the case of corals, this would be mitigating the impacts of climate change. The second approach should then be mitigating or treating the effects of more local/regional stressors such as poor water quality and/or overfishing. These approaches form part of established current reef management practices with some demonstrated successes. For example, well-managed marine protected areas can aid the resilience of reefs to climatic impacts (Mcleoda et al., 2019) and efforts in best practice localized/regional management of reefs needs to increase.

The third approach (which has been somewhat forced onto reef managers through continued declines in coral ecosystem health), is "active intervention," widely promoted and captured under the broad term of reef restoration (Boström-Einarsson et al., 2018; National Academies of Sciences, 2018). These practices range from established coral propagation and out-planting to more novel (and potentially risky) strategies such as assisted evolution (AE; Jones and Monaco, 2009; van Oppen et al., 2015). AE is a holistic term that incorporates genetic, epigenetic, and microbiome evolutionary changes, though there are other terms used in the literature including genetic or evolutionary rescue and assisted gene flow (van Oppen et al., 2017). Many restoration approaches, inclusive of AE are focused on the "individual," whether that be individual species, population or reef system and essentially represents the customized medicine approach adapted to corals and the ecosystems they inhabit. Studies answering the question of "how" corals respond to various environmental perturbations need to continue to ensure we understand the physiological responses of these organisms (Sweet and Brown, 2016). These should include (but are not limited to) studies exploring the mechanisms of interaction between the coral holobiont, its microbome and the surrounding environment, as well as genetic and epigenetic traits associated with their resilience. However, a greater focus on how such approaches can aid protection of the remaining healthy systems and devising approaches that may improve the health of degraded or damaged sites is also currently needed.

Manipulation of the coral microbiome is one approach which is being heavily discussed as a tool to aid coral resilience and if applied at the population level can have potential beneficial impacts and again be analogous to a customized medicine approach (Peixoto et al., 2017). For example, it is now well-established that *Symbiodinaceae* clades associated with corals confer varying thermal tolerance to their coral host (Berkelmans and van Oppen, 2010; LaJeunesse et al., 2010) and studies have shown this thermal tolerance to be influenced either by the host or the surrounding environmental conditions. Hence shifting or shuffling the abundance or *Symbiodinaceae* species diversity through environmentally induced changes can remove or introduce genetic material which subsequently influences metaorganism fitness (Torda et al., 2017). That said, more data is needed regarding how much these processes can be introduced and how variable they are among different coral species. Alternatively, we can be more active and physically manipulate the corals microbiome ourselves (Peixoto et al., 2017). AE of the hosts' Symbiodiniaceae population can be facilitated through the maintenance and growth of cultures under future climate scenarios. Increasing the temperature tolerance range of specific species of Symbiodiniaceae has already been achieved in controlled experiments, *ex situ*, with Cladocopium (formerly clade C1) shown to increase its thermotolerance after ∼80 generations (2.5 years) combined with superior photophysiological performance and growth when reared at 31°C compared to 27°C (Chakravarti et al., 2017). Although, there are valid concerns that manipulation of the corals' microbiome may result in decrease fitness of the metaorganism in other areas of life history (i.e., "tradeoffs"), Chakravarti et al. (2017) found no such tradeoffs in relation to calcification and growth rates measured. In non-coral hosts, similar results to Chakravarti et al. (2017) have also been achieved with coccolithophores dinoflagellates showing the ability to also become thermotolerant after repeated stress events (Flores-Moya et al., 2012; Schlüter et al., 2014). Combined, these recent studies may explain (at least in part) the observed differences in bleaching response between (and within) coral species (Abrego et al., 2008; Fisher et al., 2012).

Bacterial and archaeal communities are also important for coral fitness, likely having active roles in carbon uptake, nitrogen, and sulfur cycling plus production of antimicrobial agents thereby facilitating biological control of pathogens (Sweet and Bulling, 2017; Robbins et al., 2019). Within prokaryotes, horizontal gene transfer can facilitate rapid evolution within microbial strains, changing metabolic functions which may subsequently also confer traits to their host (Webster and Reusch, 2017). *Ex situ* trials of coral bacterial manipulation have already shown early promise (Santos et al., 2015; Rosado et al., 2019). In principle, Beneficial Microorganisms for Corals (BMCs; Peixoto et al., 2017) enhance coral fitness through either their symbiotic relationships with the host, including increasing the bioavailability of nutrients and decreasing the effect of toxic compounds or potential pathogens (biological control) or indirectly through influencing other secondary cycles in the surrounding environment that benefits the coral. These actions can be combined into BMC consortia, which contain microbial groups performing several potential beneficial functions for the coral. A guideline for the proper use and manipulation of specific putatively beneficial microbial mechanisms, combined into a mixed microbial assemblage (BMC consortia) has been postulated as a key strategy to "engineer" and enhance coral fitness and manipulate reef functions (Peixoto et al., 2017). Indeed, a recent study illustrated that the probiotic neutralization of toxic compounds (i.e., oil) was feasible with minimal negative impacts to coral health (Santos et al., 2015). Similarly, negative effects (on the host) associated with temperature stress and inoculation of pathogens have been shown to be mitigated when specific consortia of BMCs are applied in controlled experiments (Rosado et al., 2019). The search for coral probiotics is currently underway which involves the isolation and/or manipulation of coral associated bacteria and subsequent re-administration of these cultured strains to bioaugment populations (i.e., increase the numbers of specific microorganisms) that the host naturally maintains (Santos et al., 2011). However, approaches that use non-native microorganisms is also something which could be considered in the future with the caveat that a greater understanding of cellular interactions is required and the associated trade-offs associated with microbiome manipulations, combined with thorough risk/benefit analyses be conducted.

Current studies have demonstrated the ability to manipulate the corals microbiome which does appear to enhance corals thermal tolerance and disease resistance—at least in *ex situ* experiments. However there still remains a lot of unanswered questions including concerns around the biosecurity of manipulating microbes in laboratory-based settings and releasing these into the reef environment (Sweet et al., 2017). Risk assessment is paramount and can be achieved by laboratory tests, and exclusion of potential pathogens and antibiotic resistance carriers within putative BMCs cocktails. However, doing nothing also presents a risk, as global reef declines seem inevitable under future climate modeling. Therefore, an urgent need exists to develop new approaches to build the resilience of coral reefs (see **Figure 1** for a summary of some of these approaches), essentially "buying time" till climate mitigation is achieved. Many research areas are in their infancy but this field is an active and emerging research priority (e.g., National Academies of Sciences, 2018; National Academies of Science, 2019) and therefore, of great interest to the Frontiers in Marine Science community and all researchers working on coral reefs. It is paramount that we make rapid advances across multiple

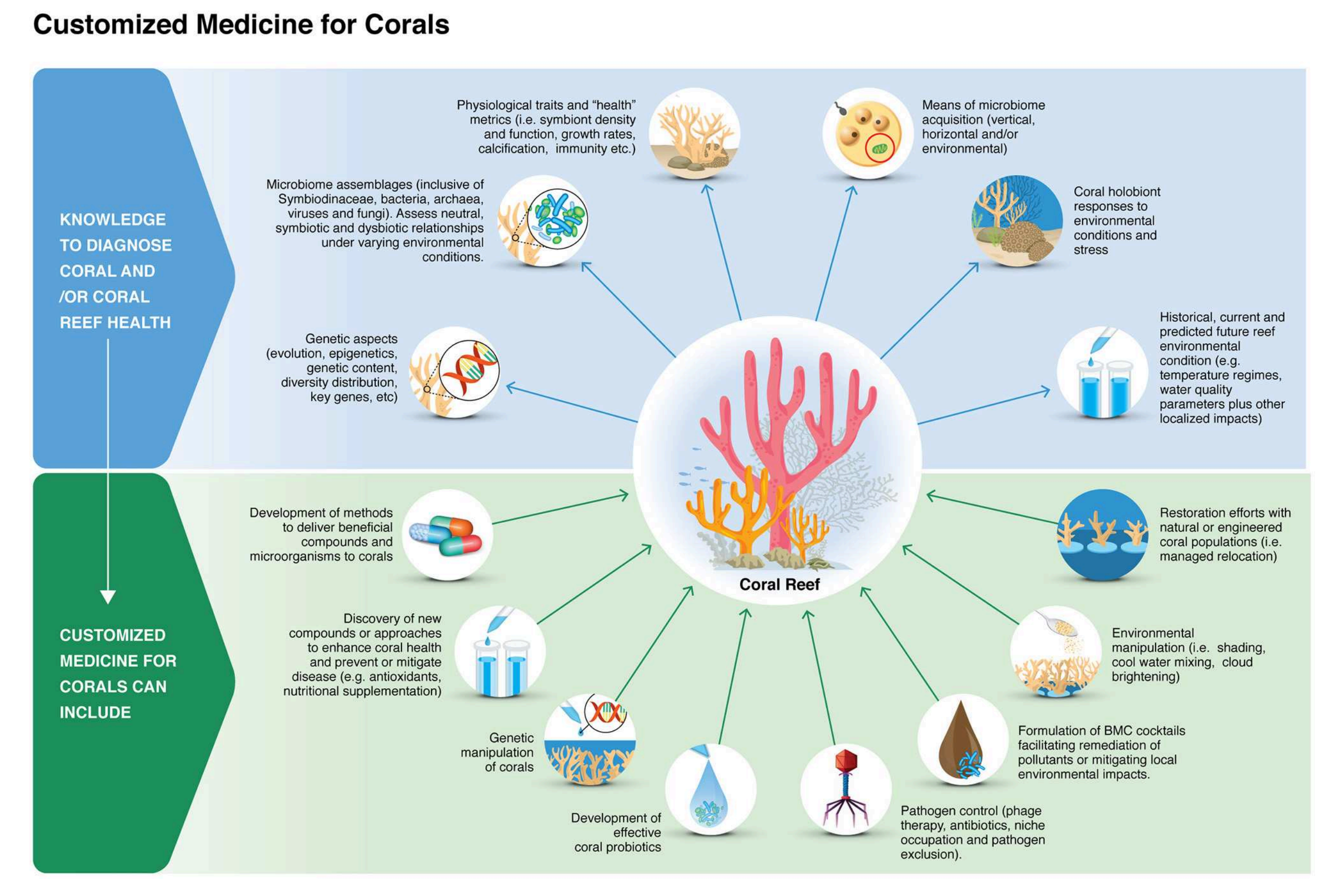

FIGURE 1 | Examples of key topics and approaches to be explored to support the development of interventions to increase coral reef resilience.

approaches (see **Figure 1**) considering the threats faced by reef ecosystems.

In conclusion, many scientists in the field of coral biology acknowledge the need for active interventions in order to stem the loss and/or declining health of reef ecosystems. However, many of these interventions or approaches need urgent and rapid development to provide toolsets helping reef managers face the declining health of these valuable ecosystems. That said, we also acknowledge that focus should certainly not be drawn away from the main causes of reef degradation i.e., climate change and localized impacts from pressures such as pollution and overfishing. Importantly, a diverse and well-managed reef ecosystem will recover faster than one impacted by localized factors when struck with a thermal anomaly (Mcleoda et al., 2019). We conclude by stating that comprehensive baseline assessments of reef health and ongoing ecosystem impacts at the reef scale are vital for designing and implementing effective measures aimed at improving reef resilience. There is no simple solution to solve the crisis faced by coral reefs and therefore studies to elucidate all parts of this gigantic puzzle on reef health, disease, adaptation, resilience, and restoration are welcome.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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