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Intestinal *Lactobacillus* in health and disease, a driver or just along for the ride?

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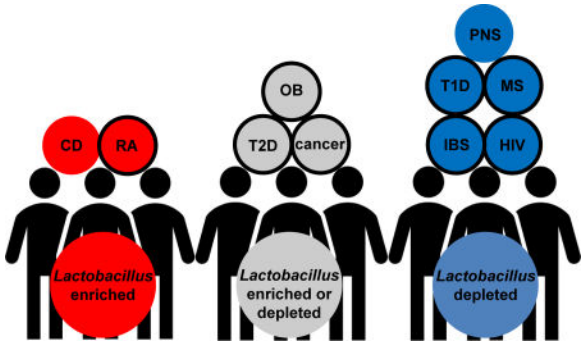
Abstract

Metagenomics and related methods have led to significant advances in our understanding of the human microbiome. Members of the genus *Lactobacillus*, although best understood for essential roles in food fermentations and applications as probiotics, have also come to the fore in a number of untargeted gut microbiome studies in humans and animals. Although *Lactobacillus* is only a minor member of the human colonic microbiota, the proportions of those bacteria are frequently either positively or negatively correlated with human disease and chronic conditions. Recent findings on *Lactobacillus* species in human and animal model microbiome research, together with the increased knowledge on probiotic and other ingested lactobacilli, have resulted in new perspectives on the importance of this genus to human health.

Graphical abstract



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Conflicts of interest

None

Introduction

Members of the genus *Lactobacillus* were long thought to be among the most abundant microorganisms in the human gastrointestinal (GI) tract and associated with good intestinal health. Following the development of culture-independent, DNA-sequence analysis methods, the numbers of autochthonous *Lactobacillus* were adjusted to ≤ 1% of the total bacterial population in the distal human gut. One consequence of this change is that the relevance of this genus to human health has come under scrutiny. In contrast, there is increased acceptance of the application of allochthonous probiotic *Lactobacillus* in fermented foods and supplements as probiotics to maintain health and prevent and treat disease [1,2]. Although human studies frequently show a benefit with probiotic administration [3], the importance of autochthonous *Lactobacillus* remains under question.

Human disease is increasingly correlated with fecal microbiota composition. Similarly, intestinal bacteria are frequently correlated with numerous other host (genetics, age) and environmental (diet, medication) factors. Such associations have been useful for identifying pathobionts associated with disease as well as taxa such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* as beneficial members of the indigenous microbiota. Similarly, a number of recent publications in which culture-independent methods were employed (e.g. 16S rRNA gene amplicon sequencing) identified *Lactobacillus* as being significantly enriched in the distal gut during either health or disease (Figure 1 and Table 1). Because these approaches are largely untargeted, the outcomes provide an unbiased perspective on the relative importance of this genus weighed against other bacterial inhabitants of GI tract. This review will address findings on the diversity and abundance of intestinal *Lactobacillus* resulting from gut microbiome studies and emerging mechanistic evidence of endogenous and ingested (probiotic) *Lactobacillus* species in the GI tract.

Abundance and diversity of intestinal *Lactobacillus*

Lactobacillus species have been isolated from the entirety of the human GI tract (oral cavity to feces) as well as the skin and vagina [4,5]. This genus is estimated to constitute 6% of the total bacterial cell numbers in the human duodenum [6] and approximately 0.3% of all bacteria in the colon [4] (Figure 2). These levels are similar to the numbers of lactobacilli found in pigs, ranging from 5 to 0.1% of total bacteria in the proximal [7] and distal [8] gut, respectively. *Lactobacillus* was found in higher quantities in rhesus macaques (up to 30% and 10% of all bacteria in the small and large intestine, respectively) [9]. Proportions of *Lactobacillus* in rodent models ranged between 30 to 60% of bacterial numbers in the ileum and approximately 25% in the colon [10,11] (Figure 2). *Lactobacillus* can also dominate the human vaginal microbiota (90–100% of total bacteria present) and is found on the skin, but in much lower relative abundance [5] (Figure 2).

Only a few out of the >200 known *Lactobacillus* species have been consistently and repeatedly associated with the human GI tract. Recently, this number was increased to over 50 *Lactobacillus* species that were repeatedly detected in the stools of healthy volunteers [•12]. The most abundant lactobacilli included *L. casei, L. delbruckeii, L. murinus, L. plantarum, L. rhamnosus*, and *L. ruminus.* Some of these species (e.g. *L. rhamnosus* and *L.*

murinus) are rarely isolated from environments outside the intestine and are considered gut-autochthonous microorganisms. Other mucosal sites are colonized by distinct species (e.g. *L. crispatus* in the vagina) [•13]. There also appears to be host-specificity among some *Lactobacillus* species, as shown for linages of *L. reuteri* [14].

Infectious disease

Both human immunodeficiency virus (HIV) - infected humans and simian immunodeficiency virus (SIV) - infected rhesus macaques harbor reduced numbers of intestinal *Lactobacillus* [15,16] (Table 1). *Lactobacillus* depletion in rhesus macaques was associated with the loss of gut barrier-promoting T-helper 17 (Th17) cells and increased microbial translocation [16]. The potential of *Lactobacillus* to prevent or reverse intestinal damage during infection was demonstrated with the reduced interleukin-1β-mediated inflammation and improved barrier function upon inoculation of *L. plantarum* directly into ileal loops of SIV+ macaques shortly after SIV infection [17]. The intestinal epithelium in healthy animals responded similarly to *L. plantarum*, consistent with the finding that the ileal transcriptomes of *L. plantarum* were indistinguishable between SIV+ and SIV− animals [18]. In human populations, HIV+ patients on a multi-strain probiotic supplement exhibited higher numbers of memory Th17 cells in peripheral blood and in the intestine, and histological examination of colonic biopsies indicated increased intestinal barrier function [19].

Several recent animal studies have indicated a broader role for *Lactobacillus* in prevention and resolution of infectious disease. Tryptophan metabolites (indole aldehydes) produced by indigenous *L. reuteri* strains activate host aryl hydrocarbon receptors (AHR) to promote gut and vaginal epithelial barrier and antimicrobial responses required for limiting the expansion of *Candida albicans*, an opportunistic pathogen [••20]. Autochthonous *Lactobacillus* might also have a role in the resolution of infectious disease and recovery of immune homeostasis. Although *Yerstina enterocolitica* infection was cleared from toll-like receptor 1 (TLR1) knockout mice, the intestine was activated towards an inflammatory phenotype and the gut microbiota was enriched with *Desulfovibrionaceae* while containing lower numbers of *Lactobacillus* [••21]. Oral gavage with *L. reuteri* reduced anti-commensal antibodies, innate cytokines, and Th17 responses; thereby ameliorating immune hyper-reactivity [••21]. Conversely, post-*Yersinia pseudotuberculosis* infection lactobacilli were cultured from enlarged gut-associated lymphoid tissue and were associated with chronic lymphadenopathy, indicating that these bacteria might contribute to chronic, immune hyper-reactivity [22].

Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD)

A meta-analysis of reports investigating the fecal microbiomes from IBS patients and healthy subjects concluded *Lactobacillus* was depleted in diarrhea-dominant, IBS patients [23] (Table 1). Another meta-analysis of IBS cohort studies determined that intestinal *Lactobacillus* was depleted in all cases of IBS in Chinese patients, but this association was not found or was reversed in patients from other countries [24]. Consistent with these results, meta-analysis of probiotic intervention studies (43 randomized controlled trials

(RCTs)) for treatment of IBS concluded that multi-species probiotics diminish symptoms (abdominal pain, bloating, and flatulence scores) [25].

Conversely, intestinal abundance of *Lactobacillus* and other genera including *Bifidobacterium* were recently positively correlated with Crohn's disease (CD) patients [26,27] (Table 1). In both studies, *Lactobacillus* enrichment coincided with depletion of *F. prausnitzii*. Whether *Lactobacillus* is participating in disease or is simply adapted to survive the pro-inflammatory gut environment is not known. These findings contrast with ulcerative colitis (UC) in which probiotic *Lactobacillus* consumption has been associated with improved clinical symptoms [28]. *Lactobacillus* might be particularly supportive in CD and UC patients with caspase recruitment domain family member 9 (CARD9) risk alleles whose microbiome has a reduced production of AHR ligands [••29]. Consistent with this possibility, intestinal inflammation in CARD9 knockout (KO) mice was attenuated after inoculation of mice with *Lactobacillus* strains capable of metabolizing tryptophan [••29].

Rheumatoid arthritis (RA)

The intestinal microbiota of patients with severe and early onset RA were shown to have increased proportions of *L. salivarius, L. ruminus*, and *L. iners* when compared to healthy, age-matched individuals [•30] (Table 1). Enrichment of *Lactobacillus* spp. was also observed in collagen-induced, arthritic mice [31]. These results are in opposition to recent RCTs of probiotics in RA patients. In one study, patients consuming *L. casei* showed reduced disease activity scores, higher quantities of serum IL-10, and decreased levels of serum TNFα, IL- 6 and IL-12 compared to placebo [32]. The other RCT concluded that a mixed strain probiotic supplement significantly improved disease activity scores and lowered levels of serum C-reactive protein (CRP) [33]. Such findings might indicate species or strain-specific differences between autochthonous and allochthonous *Lactobacillus* on RA disease activity.

Type 1 Diabetes (T1D)

The proportions of *Lactobacillus* were lower in adults with T1D than healthy, first-degree relatives and unrelated healthy individuals according to untargeted 16S rRNA analysis [•34] (Table 1). A similar reduction in *Lactobacillus* was observed in children with T1D [35] (Table 1). Interestingly, children exposed to probiotic *Lactobacillus* early in life were found to have a significantly reduced risk of developing islet autoimmunity [36]. It is not yet understood how *Lactobacillus* could be regulating islet beta-cell auto-immunity, although it has been suggested that a lack of intestinal lactate-producing bacteria depletes butyrate-producing taxa leading to aberrant immune responses [35].

Multiple sclerosis (MS)

A cohort study found that the relative abundance of intestinal *Lactobacillus* was lower in MS patients compared to healthy adults [37] (Table 1). Similar depletions in intestinal *Lactobacillus* were observed in a pre-clinical, rodent model of MS [38]. Consistent with a benefit of *Lactobacillus* in this autoimmune disease were the findings from a recent RCT of MS patients, whereby consumption of a multi-species probiotic improved the expanded

disability status score, self-reported depression, anxiety and stress, as well as decreased serum CRP compared to placebo [39]. Because circulating levels of AHR ligands are lower in MS patients compared to healthy adults [40], *Lactobacillus* might be useful for the maintenance or replenishment of these compounds. To this regard, *Lactobacillus*-produced indole aldehydes had a potent anti-inflammatory effect on brain glial cells (astrocytes) to limit central nervous system inflammation in a mouse model of human MS [•41].

Obesity and Type 2 Diabetes (T2D)

There are conflicting reports on the association of intestinal *Lactobacillus* with obesity in humans [42–45] (Table 1). Likewise, initial studies found increased levels of *Lactobacillus* in patients with T2D [46], although this trend was eliminated or reversed when controlling for metformin treatment [47] (Table 1). Also contrary to these results, meta-analysis of RCT studies found that probiotic *Lactobacillus* improved weight management outcomes in obese adults [48]. Consumption of yogurt and other dairy products fermented by *Lactobacillus* is also significantly associated with protection from T2D and obesity (recently reviewed in [2]).

Because *Lactobacillus* species appear to be either associated with weight gain or weight loss [49], the disparate findings among obese individuals might be due to genetic differences among the lactobacilli. Strain and species distinctions could result in variations in carbohydrate metabolism and production of fermentation end-products, such as lactate [50]. The production of bile salt hydrolases is another distinguishing feature of some *Lactobacillus* species, and this activity is responsible for significantly altering the activation of farnesoid x receptor (FXR) signaling and hepatic lipid metabolism [51,52].

Cancer

In a systematic review of thirty-one studies, *Lactobacillus* along with a limited number of butyrogenic genera were consistently diminished in colorectal cancer patients [53] (Table 1). Preventative and therapeutic roles of *Lactobacillus* in cancer are supported in studies with pre-clinical, rodent models, including a recently study in which a multi-strain probiotic altered Th-cell polarization away from Th17 cells in a mouse model of hepatocellular carcinoma [54]. However, *Lactobacillus* might not always be beneficial in certain extra-intestinal sitesas shown by the higher levels of *Lactobacillus* found in malignant breast cancer compared to benign-disease tissues [55]. There was also a positive association between the levels of this genus in the oral microbiome and head and neck squamous cell carcinoma [56] (Table 1).

Cognitive development and behavior

Maternal prenatal stress might influence the infant microbiome, potentially damaging cognitive development. In humans, prenatal cortisol concentrations were inversely correlated with infant levels of intestinal *Lactobacillus* and *Lactococcus*, whereas *Proteobacteria* were enriched [•57] (Table 1). A comparable depletion of *Lactobacillus* was observed in rodent models of prenatal stress, with the microbiome of the offspring remaining disrupted into

adulthood [58]. Prenatal low-dose penicillin [59] or high fat diet [••60] could similarly induce long-term dysbiosis and behavioral deficits in mice. These deficits could be prevented by concurrent administration of *Lactobacillus*-containing probiotics to the dam [59] or by indigenous *L. reuteri* to offspring [••60].

In adult mouse models of microbiota-gut-brain axis deficits, administration of *Lactobacillus*-containing probiotics was found to beneficially impact both cognition and colonic function, while reverting intestinal dysbiosis [61,62]. Such results might also be relevant to emotional disorders and this is supported in probiotics studies which have indicated that probiotic *Lactobacillus* might improve symptoms of human depression [63,64]. Therefore, beneficially modulating the microbiota using *Lactobacillus* can impact the microbiota-gut-brain axis and should be more thoroughly studied in human mother-infant cohorts.

Conclusions

Our increased understanding of intestinal *Lactobacillus* from untargeted microbiome studies supports the premise that general properties conferred by this genus have far-reaching consequences on human health. Such knowledge could be further advanced via studies designed to determine the proximity of *Lactobacillus* to the intestinal epithelium or which focus attention on other sites on the body wherein members of this genus can constitute the majority of bacteria present (e.g. vagina). However, even without this information, strain and/or species-specific differences (e.g. tryptophan and bile metabolism) might be useful to explain variations in the involvement of this genus, either in the prevention or mitigation of disease or, alternatively, as a contributing factor to disease outcomes. Furthermore, the notable variation in intestinal abundance of this genus between healthy and diseased, or health-compromised, individuals indicates that *Lactobacillus*, or at least certain species or genotypes of *Lactobacillus*, could be useful gut biomarkers. These considerations can also inform the improved development and use of probiotics in different human populations.

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Highlights

- Intestinal lactobacilli are often detected in untargeted, gut microbiome studies.
- Depletion of intestinal *Lactobacillus* is frequently associated with disease.
- Probiotics use is supported by findings on indigenous *Lactobacillus* populations.
- Tryptophan metabolism is an emerging, beneficial trait of intestinal lactobacilli.

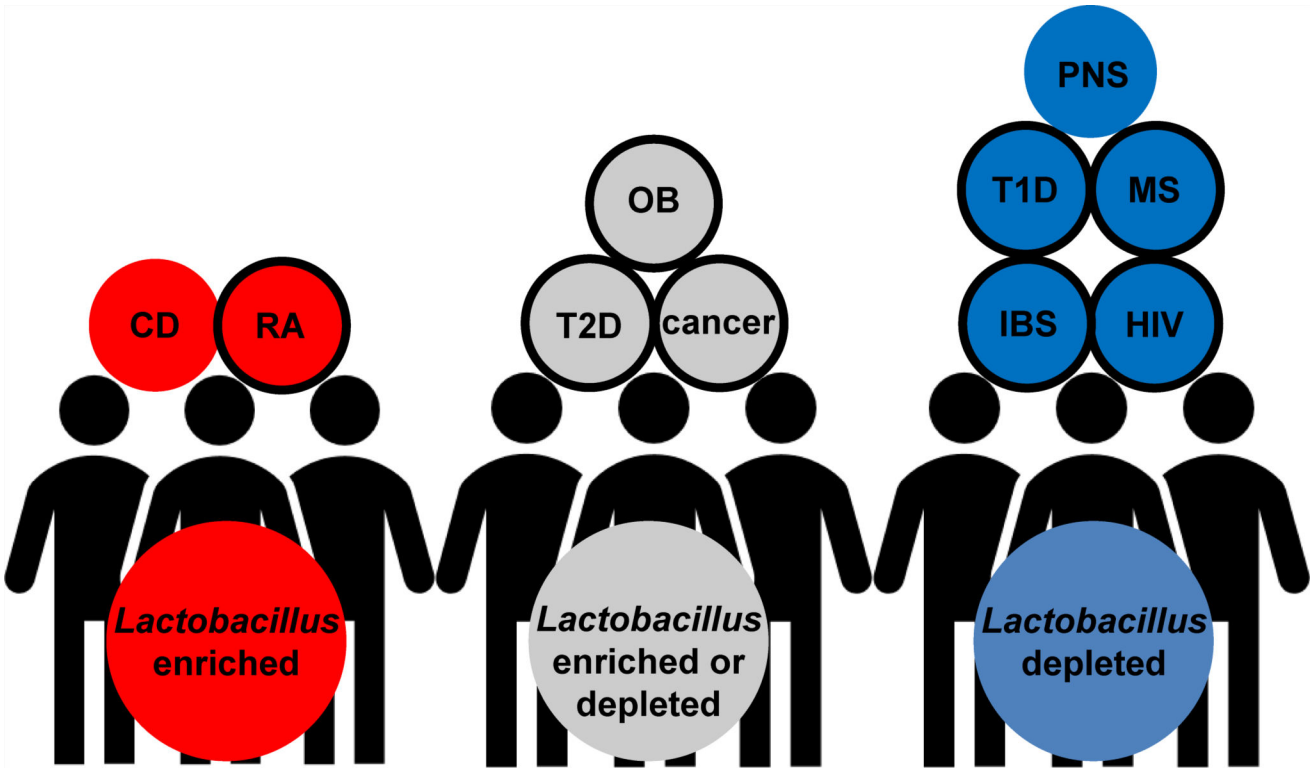

Figure 1. Alteration of intestinal *Lactobacillus* in health and disease

Blue circles indicate *Lactobacillus* is depleted in disease compared to healthy controls. Red circles indicate *Lactobacillus* is increased in disease. Grey circle indicates *Lactobacillus* is either increased or decreased. Circles with black edges indicate a benefit for consumption of probiotics for treating disease. CD = Crohn's disease, RA = rheumatoid arthritis, OB = obesity, T2D = type 2 diabetes, IBS = irritable bowel syndrome, T1D = type 1 diabetes, PNS = prenatal stress, HIV = human immunodeficiency virus, MS = multiple sclerosis.

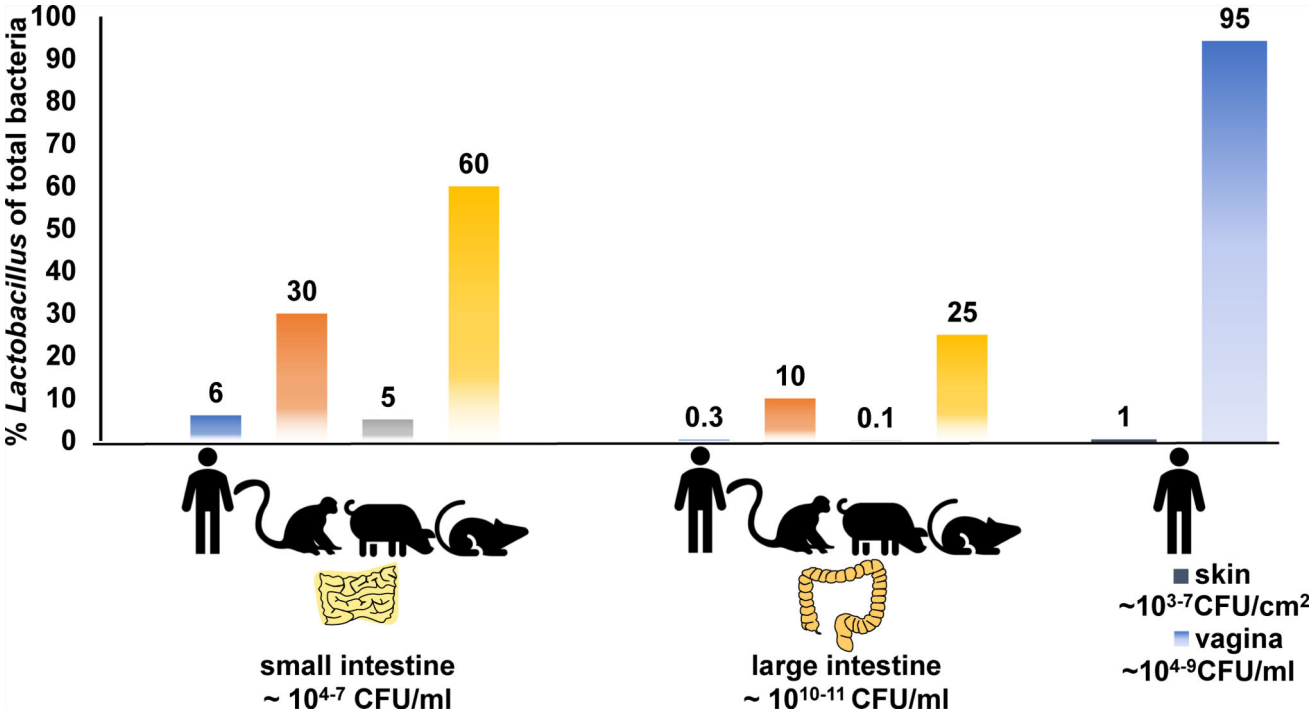

Figure 2. Relative abundance of *Lactobacillus* in humans and animals

Numbers underneath anatomical locations indicate estimates for total bacterial community cell numbers.

Table 1

Recent human studies analyzing microbiomes in health and disease.

Disease/Condition	Study design[a]	*Lactobacillus* proportions[b]	*Lactobacillus* species[c]	Method[d]	Reference
IBS	meta-analysis 13 studies	↓		qRT-PCR	[23]
	meta-analysis 10 Chinese studies	↓		fecal bacterial counts	[24]
	meta-analysis 7 global studies	−		fecal bacterial counts	[24]
CD	28 CD, 26 HC	↑		metagenomics	[26]
	15 CD, 21 HC	↑		qRT-PCR	[27]
HIV	8 infected, 8 HC	↓		16S rRNA	[15]
Reumatoid Arthritis	77 RA, 80 HC	↑	*L. salivarius, L. ruminus, L. iners*	metagenomics	[30]
Type 1 Diabetes	21 T1D, 32 HC	↓		16S rRNA	[34]
	28 T1D, 27 HC	↓		16S rRNA microarray	[35]
Multiple Sclerosis	31 MS, 36 HC	↓		16S rRNA	[37]
Obesity	15 obese, 17 HC	↓	*L. plantarum*	qRT-PCR	[45]
	30 obese, 24 OW, 30 HC	↑		qRT-PCR	[42]
	42 obese, 36 HC	−		16S rRNA	[43]
	67 obese, 67 HC	−		16S rRNA	[44]
Type 2 Diabetes	53 T2D, 43 HC	↑	*L. gasseri*	16S rRNA	[46]
	93 Met+T2D, 106 Met−T2D, 554 HC	↓		metagenomics	[47]
Colon cancer	systematic review 31 studies	↓		16S rRNA	[53]
Breast cancer	17 BC, 16 BD	↑		16S rRNA	[55]
Head and neck squamous cell cancer	17 HNSCC, 25 HC	↑		16S rRNA	[56]
Prenatal stress	56 mother-infant pairs	↓		16S rRNA	[57]

[a] CD = Crohn's disease, HC = healthy control, OW = overweight, Met+T2D = metformin treated type 2 diabetes patients, Met−T2D = patients not treated with metformin, BC = breast cancer, BD = benign disease, HNSCC = head and neck squamous cell cancer

[b] Proportions or numbers of *Lactobacillus* were lower (↓),higher (↑), or unchanged (−) in individuals with disease or chronic conditions compared to healthy individuals

[c] Species identification was conducted by authors and not assessed by reviewers

[d] qRT-PCR = quantitative real time-PCR of 16S rRNA, metagenomics = shotgun whole genome sequencing, 16S rRNA = 16S ribosomal RNA sequencing