Chemotherapy-Induced Diarrhea Evaluation Table 2023: Probiotics

Systematic Review

Citation	Design/Method Sample/Setting	Variables and Intervention	Outcome Measures	Results/Analysis	Limitations	Quality and Nursing Implications
Danis, R., Mego, M., Antonova, M., Stepanova, R., Svobodnik, A., Hejnova, R., & Wawruch, M. (2022). Orally administered probiotics in the prevention of chemotherapy (± radiotherapy)-induced gastrointestinal toxicity: A systematic review with meta-analysis of randomized trials. *Integrative Cancer Therapies, 21*, 15347354221144309. https://doi.org/10.1177/15347354221144309	**Design:** Systematic review and meta-analysis **Methods:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Search of MEDLINE®, Web of Science®, and Scopus® databases for articles published from 1990 to 2020 about randomized controlled trials of diarrhea outcomes in patients receiving chemotherapy with or without radiation therapy and probiotics. **Sample:** Eight studies (six randomized controlled trials) with 697 participants with gynecologic, colorectal (CRC), thoracic, or esophageal cancers who received cisplatin, oxaliplatin, 5-fluorouracil, or capecitabine. In the intervention group, 400 participants used probiotics; in the control group, 297 participants did not use probiotics. **Setting:** Trials across multiple countries	**Independent Variable(s):** Probiotic use during chemotherapy with or without radiation therapy **Dependent Variable(s):** Incidence of grade 3 or 4 diarrhea Incidence of all-grade diarrhea Use of rescue medication	Common Terminology Criteria for Adverse Events (CTCAE version 2.0, version 3.0 version 4.0, version 4.1 used in different studies) World Health Organization (WHO) criteria for diarrhea measurement.	Probiotics reduced risk of grade 3 or 4 diarrhea by 78% in studies with low risk of bias with total of 114 participants (risk ratio (RR) = 0.22, 95% CI [0.05, 1.08]; p = 0.06) This reduction was not statistically significant. Overall diarrhea risk was reduced by 36% in patients receiving probiotics (RR = 0.64, 95% CI [0.48, 0.86]; p = 0.003). In a sensitivity analysis including 2 studies, probiotics reduced the need for rescue medications by 32% compared with control (RR = 0.68, 95% CI [0.46, 1.00]; p = 0.05). In a subgroup analysis, probiotics reduced the risk of grade 3 and 4 diarrhea development in patients with colorectal cancer (RR = 0.56 95% CI [0.34, 0.92), p = 0.02).	Clinical heterogeneity in cancer types and chemotherapy regimens Probiotic administration variability in strain and dosing Variability in diarrhea assessment tool use Low number of studies and sample sizes in included studies Potential publication bias	Although the methods were sound, further studies need to be conducted to demonstrate clinical benefit for the use of probiotics in patients experiencing chemotherapy-induced diarrhea with or without radiation therapy. Certain probiotics could provide mild benefit to certain patients experiencing chemotherapy-induced diarrhea. Findings show that although probiotics may not demonstrate a statistically significant benefit, they may demonstrate a clinical significance that warrants further exploration.

Deleemans, J.M., Gajtani, Z., Baydoun, M., Reimer, R.A., Piedalue, K.A., & Carlson, L.E. (2021). The use of prebiotic and probiotic interventions for treating gastrointestinal and psychosocial health symptoms in cancer patients and survivors: A systematic review. *Integrative Cancer Therapies, 20,* 15347354211061733. https://doi.org/10.1177/15347354211061733	**Design:** Systematic review **Methods**: Search of PubMed®, MEDLINE®, CINAHL®, PsychINFO, Web of Science®, ClinicalTrials.gov, American Society of Clinical Oncology, European Society for Medical Oncology , OAIster, and Google Scholar for studies on prebiotic or probiotic use and gastrointestinal (GI) health outcomes. Multiple treatment modalities were examined, including chemotherapy, radiation therapy, and surgery. 12 of 974 articles were included in the systematic review; 10 randomized controlled trials and 2 pre–post single group design. The National Institutes of Health Quality Assessment Tools were used to evaluate the quality of these articles. **Sample**: 12 studies; participants were 974 patients, with a mean age of 58 years, and with a variety of cancer types and treatment modalities represented. 10 of the 12 studies reported on participants who were receiving active cancer treatment. **Setting**: Oncology settings during and/or after cancer directed therapies	**Independent Variable(s):** Use of prebiotics, probiotics, or a combination of both during and/or after cancer-directed therapies. **Dependent Variable(s):** GI symptoms such as diarrhea, constipation, abdominal pain, and bloating, and psychosocial symptoms such as quality of life (QOL), anxiety, and depression	Various scales used for measurement of multiple symptoms including: CTCAE Memorial Sloan Kettering Bowel Function Instrument European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 Gastrointestinal Quality of Life Index Radiation Therapy Oncology Group Toxicity Scale SF-36® Wexner Constipation Scoring System	Narrative analysis outlined studies that found statistically significant improvements in gastrointestinal symptoms (n = 11). 4 studies found improvements in QOL outcomes, fatigue, anxiety, and depression in the probiotic group compared with controls.	Cancer-directed treatment modalities across studies were heterogenous. A variety of strategies were used for probiotic and prebiotic dosing, frequency, timing, and duration of administration. A variety of outcome measurement tools were used between studies, making determination of effect sizes difficult.	The rigor of the studies' quality evaluation was sound. Methods for study inclusion and exclusion were consistent, and the literature search was comprehensive. Limitations of findings included how and when to dose and administer probiotics and prebiotics in order to apply to clinical practice. The most common probiotic strains were from the genus *Lactobacillus*, followed by *Bifidobacterium*. Prebiotics and probiotics appear to be helpful in reducing the incidence of diarrhea, bloating, constipation, and abdominal pain. There is also evidence that taking prebiotics and/or probiotics increase QOL. However, there is no clarity about the type of prebiotics and probiotic to use, recommended dosage, or recommended frequency. The current review does not provide strong enough evidence to recommend this as a strategy for supportive care. More data are needed on the type, frequency, and dosage of prebiotics and probiotics, as well as on their usefulness for chemotherapy-induced diarrhea.

Hassan, H., Rompola, M., Glaser, A.W., Kinsey, S.E., & Phillips, R.S. (2018). Systematic review and meta-analysis investigating the efficacy and safety of probiotics in people with cancer. *Supportive Care in Cancer*, *26*(8), 2503–2509. https://doi.org/10.1007/s00520-018-4216-z	**Design:** Systematic Review and Meta-Analysis **Methods:** Database search: MEDLINE®, Embase®, and AMED for RCTs investigating the efficacy of probiotics as an intervention for gastrointestinal-associated effects. Additional studies and case reports included for safety analysis. Dual screening and data extraction. Cochrane risk-of-bias tool used. Loke method used for quality assessment. **Sample:** 21 RCTs included in efficacy analysis, 25 non-RCTs and case reports used for safety analysis. N = 2,982 for efficacy and 2,242 for safety. Sample range across safety studies was 10–205. Sample range across efficacy studies was not reported in supplement. Sample included pediatric to adult patients receiving chemotherapy or RT and probiotics as an intervention. **Setting:** RT (n = 9 studies), chemotherapy (n = 7 studies), and surgical intervention (n = 11 studies) in 14 different countries, primarily China	**Independent Variable(s):** Probiotics **Dependent Variable(s):** Efficacy measured incidence of diarrhea and duration of pyrexia with use of probiotics. **Intervention:** Probiotics	Incidence of diarrhea, pyrexia duration, severity of diarrhea, and septicemia, central line infections.	Reduction incidence of diarrhea with use of probiotics (5 studies, n = 496) (OR = 0.52, 95% CI [0.34, 0.78], I2 = 36.9%). Reduced duration of pyrexia with use of probiotics (5 studies) (mean difference = 0.39 days, 95% CI [0.35, 0.43], I2 = 0.01%). 25 studies reviewed in safety analysis of probiotics: data of AEs inconclusive and not consistent to determine safety.	Limited number of studies High heterogeneity Limited search Limited data in pediatrics	Rigorous systematic review, inconclusive evidence on AEs and quality concerns limiting applicability. Chemotherapy and RT can alter gut flora. Diarrhea is a common side effect from many chemotherapy and RT treatments. Probiotics may be beneficial in decreasing diarrhea and grade of diarrhea, and potentially reducing pyrexia. Insufficient data and guidelines exist to support specific recommendations. More data are needed on AEs.

Miarons, M., Roca, M., & Salvà, F. (2021). The role of pro-, pre- and symbiotics in cancer: A systematic review. *Journal of Clinical Pharmacy and Therapeutics*, *46*(1), 50–65. https://doi.org/10.1111/jcpt.13292	**Design:** Systematic Review **Methods:** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). MEDLINE search for placebo-controlled randomized controlled trials; quality evaluation was done using the Cochrane Risk of Bias tool and Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. **Sample:** Across 22 studies, 2,287 patients with various cancer types, including colorectal (CRC), esophageal, prostate, gastric, nasopharyngeal, pelvic, and periampullary cancer. The majority of studies (22) were in CRC patients. Patients were treated with prebiotics, probiotics and symbiotics. **Setting:** 12 studies were in surgical settings, 5 studies were in chemotherapy settings, 4 studies were in radiation therapy settings, and 1 study was in a combined chemotherapy and radiation therapy setting.	**Independent Variable(s):** Use of prebiotics, symbiotics, and probiotics. **Dependent Variable(s):** Many variables and outcomes were examined in this broad review of microbial therapies on adverse events (AEs)of cancer treatments. Most covered diarrhea incidence, severity, and duration, and infectious complications **Intervention:** Probiotic (10 studies), Symbiotics (7 studies), Prebiotics (5 studies) different strains and dosages across studies, most using more than single strain of bacteria	CTCAE grading of severity of diarrhea Intervention effects on incidence, severity, and duration of diarrhea	Reported across all modalities: Diarrhea incidence in intervention groups ranged from 3.2% to 39.1%. Diarrhea incidence in control groups ranged from 6.7% to 60.9% Frequency of CTCAE grade 3 or higher diarrhea (3 randomized controlled trials only) in intervention groups ranged from 8.64% to 39.1%. Frequency of CTCAE grade 3 or higher diarrhea (3 randomized controlled trials only) in control groups ranged from 15.7% to 60.9%. Diarrhea incidence in 4 studies favored the intervention group, with statistical significance.	High heterogeneity of studies and low sample sizes in most of the studies; no subgroup analysis or meta-analysis was able to be performed. Only one database was used in the evidence search	The heterogeneity and scarcity of studies and the broad range of prebiotics, probiotics, and symbiotics studied means that practitioners are still challenged to know definitively whether prebiotics, probiotics, and symbiotics should be ordered for any given patient. Despite this, the use of randomized controlled trials in this review increases the strength of its conclusions. The studies examined in this systematic review looked at many adverse effects across many treatment modalities. Although sample sizes were generally small for chemotherapy- and radiation therapy–induced diarrhea, it appears that probiotics and symbiotics are generally safe and may be helpful in reducing the incidence of diarrhea. More research is needed on this intervention.

Wardill, H.R., Van Sebille, Y.Z.A., Ciorba, M.A., & Bowen, J.M. (2018). Prophylactic probiotics for cancer therapy-induced diarrhoea: A meta-analysis. *Current Opinion in Supportive and Palliative Care*, *12*(2), 187–197. https://doi.org/10.1097/SPC.0000000000000338	**Design:** Systematic Review and Meta-Analysis **Methods:** PRISMA. Database search: PubMed®, Embase®, CINAHL®, and CENTRAL for studies investigating probiotic interventions for any cancer therapy and effect on diarrhea outcomes. Dual screening and data extraction, risk-of-bias analysis. **Sample:** 7 RCTs included 1,091 participants across studies with sample range of control group 23-239 and probiotic group 23-243. Adults aged 18 years or older with gynecologic, colorectal, and lung cancer. **Setting:** Treatment with radiation, chemotherapy and radiation therapy, chemotherapy, and targeted therapy	**Independent Variable(s):** Prophylactic probiotics for gastrointestinal side effects **Dependent Variable(s):** Incidence of diarrhea, severe diarrhea, and use of rescue medications **Intervention:** A range of probiotic formulations were used in the studies; the majority contained Lactobacillus strains.	Incidence of diarrhea Incidence of severe diarrhea (grade 3 or greater) measured using CTCAE scale of chemotherapy-induced diarrhea Use of rescue medications	Overall incidence of diarrhea (6 studies): RR = 0.81, 95% CI [0.6, 1.09], p = 0.1.6 Prevention of severe diarrhea: RR = 0.54, 95% CI [0.25, 1.16] p = 0.11. Use of rescue medications (3 studies): RR = 0.93, 95% CI [0.53, 1.65], p = 0.81.	Small number of RCTs with high heterogeneity Potential publication bias	Findings are clinically relevant and can be easily understood. Findings of this meta-analysis on the use of probiotics on broad diarrhea prevention revealed no significant differences in overall incidence of diarrhea, prevention of diarrhea, or use of rescue medications. Consistent, standardized, and objective measures for diarrhea are needed and should be sought when documenting cancer treatment–related diarrhea.

Wei, D., Heus, P., van de Wetering, F.T., van Tienhoven, G., Verleye, L., & Scholten, R.J. (2018). Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer. *Cochrane Database of Systematic Reviews*, *8*(8), CD008831. https://doi.org/10.1002/14651858.CD008831.pub3	**Design:** Systematic Review and Meta-Analysis **Methods:** Systematic review of RCTs. Database search of CENTRAL, MEDLINE®, Embase®, ClinicalTrials.gov, and International Clinical Trials Registry Platform for studies of probiotics with or without intervention comparison for the treatment of RT with or without chemotherapy-induced diarrhea. Dual screening and data extraction. Cochrane risk-of-bias tool used. **Sample:** 12 studies (N = 1,554 participants); 11 studies were prevention (7 with placebo comparison) **Setting:** Secondary care setting, RT with or without chemotherapy	**Independent Variable(s):** Probiotics versus placebo **Dependent Variable(s):** RT with or without chemotherapy–induced diarrhea (any diarrhea, grade 2 or higher diarrhea, grade 3 or higher diarrhea), required rescue medications for diarrhea	**Primary:** Proportion of participants with diarrhea in prevention studies, reduction in severity of diarrhea in treatment studies using CTCAE, quality of life validated scales **Secondary:** Severity of diarrhea in prevention studies, time to rescue medications for diarrhea, use of rescue medications, AEs, diarrhea-related mortality (grade 3 or 4 at time of death)	Proportion of participants with diarrhea (probiotics vs. placebo): RT alone (1 study, N = 482) (RR = 0.35, 95% CI [0.26, 0.47]). Chemotherapy and RT (N = 63; no significant differences) (RR = 1, 95% CI [0.94, 1.06]), Standard vs. high dose RT (N = 167; RR = 0.92, 95% CI [0.82-1.02] versus RR = 0.89, 95% CI [0.78-1.02]). Quality of life: no significant differences. Findings in 4 studies of probiotics (N = 420) examining Grade 2 or greater diarrhea with radiation therapy with or without chemotherapy were not statistically significant, (RR = 0.75, 95% CI [0.55, 1.03]). Findings in 3 studies of probiotics (N = 793) examining Grade 3 or greater diarrhea with radiation therapy with or without chemotherapy were not statistically significant, (RR = 0.11, 95% CI [0.11, 1.24] and noted high heterogeneity (I2 = 91%). Findings in 3 studies (N = 194) examining use of rescue medications for diarrhea in probiotic versus placebo groups were not statistically significant (RR = 0.50, 95% CI [0.15, 1.66]).	Heterogeneity between studies, high risk of bias mainly associated with nonblinded studies, detection bias, and insufficient information	Evidence was inconclusive on probiotics and prevention and treatment of RT- or chemotherapy-induced diarrhea. Evidence was low to very low certainty. No severe side effects were observed in the probiotics group. Evidence on the use of probiotics for prevention and treatment of RT- and/or chemotherapy-induced diarrhea was low or very low certainty with high risk of bias. More well-powered RCTs with uniform outcome measures are needed to draw conclusions on benefits. Nurses can use these results to discuss findings with patients and other healthcare professionals.

General Evidence

Citation	Design/Method Sample/Setting	Variables and Intervention	Outcome Measures	Results/Analysis	Limitations	Quality and Nursing Implications
Huang, F., Li, S., Chen, W., Han, Y., Yao, Y., Yang, L., . . . Deng, X. (2023). Postoperative probiotics administration attenuates gastrointestinal complications and gut microbiota dysbiosis caused by chemotherapy in colorectal cancer patients. *Nutrients, 15*(2), 356. https://doi.org/10.3390/nu15020356	**Design:** Randomized placebo controlled prospective study **Methods:** Participants took either probiotics (containing the 4 strains *Bifidobacterium infants*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus*) or placebo three times daily, from three days post-operatively through the first chemotherapy cycle. **Sample:** Patients (N = 100) with colorectal cancer (CRC) treated with radical surgery and receiving chemotherapy (n = 50 in the intervention group and n = 50 in the control group). **Setting:** Single institution (Hospital of Nanchang University, China)	**Independent Variable(s):** Probiotic (containing the 4 strains *B.infantis*, *L. acidophilus*, *E. faecalis*, and *B. cereus*) **Dependent Variable(s):** Gastrointestinal adverse effects of chemotherapy, including nausea, acid reflux, abdominal pain, abdominal distention, constipation, diarrhea, and gut microbiome dysbiosis production of short chain fatty acids (SCFAs) **Intervention:** Participants took either probiotics (containing the 4 strains *B.infantis*, *L. acidophilus*, *E. faecalis*, and *B. cereus*) three times daily, from 3 days postoperatively through the first chemotherapy cycle or placebo on the same schedule.	Recording of patient's GI symptoms Fecal samples for detection of SCFAs	Patients in the probiotics arm had significantly reduced abdominal pain (3% in probiotic group, 12% in control group; p = 0.025), less abdominal distention (5% in probiotic group, 14% in placebo group; p = 0.041), less constipation (4% in probiotic group, 14% in placebo, p=0.019), and less diarrhea (8% in probiotic group, 20% in placebo group p=0.008). Probiotics were also helpful in decreasing the disruption of the gut microbiota diversity, reshaping the disturbed gut bacterial populations, and decreasing the production of SCFAs.	Single center Probiotics were manufactured at the study institution. Limited to patients with CRC The method for monitoring symptoms is not fully described.	Methodology is sound and the study results are reliable and reproduceable. The results could be applied to all patients with CRC but may not be generalizable to other cancer types. More data are needed on standardization of probiotics used and results in other cancer types.

Lin, S., & Shen, Y. (2020). The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: A systematic review and meta-analysis based on 23 randomized studies. *International Journal of Surgery*, *84*, 69–77. https://doi.org/10.1016/j.ijsu.2020.10.012	**Design:** Systematic Review and Meta-Analysis **Methods:** Database search: Cochrane Library, PubMed®, Embase®, Web of Science®, Chinese National Knowledge Infrastructure, Wanfang, and VIP for studies evaluating the safety and efficacy of probiotic use for chemotherapy and radiation-induced diarrhea. Dual screening and data extraction. Cochrane risk-of-bias tool used. **Sample**: 23 studies (RCTs and non-RCTs included); 2,570 patients included in the review. Sample range across studies 24–490. Patients with a diagnosis of abdominal or pelvic cancer receiving RT, chemotherapy, or concurrent therapy and probiotics or placebo. **Setting:** Radiation facilities	**Independent Variable(s):** Probiotic supplementation **Dependent Variable(s):** Incidence of all grades of chemotherapy and radiation-induced diarrhea Response rate Adverse events from probiotics Antidiarrheal use on Bristol Stool Form Scale	CTCAE Bristol Stool Form Scale	Meta-analysis included 16 RCTs reporting efficacy of intervention. The incidence of all diarrhea (RR = 0.16, 95% CI [0.51, 0.73]), grade 3 or greater diarrhea (RR = 0.36, 95% CI [0.18, 0.72]), and grade 2 or greater diarrhea (RR = 0.65, 95% CI [0.54, 0.78]), but not that of less than grade 2 diarrhea (RR = 1.07, 95% CI [0.95, 1.21]), was significantly reduced in the probiotics compared to the placebo groups. The incidence of chemotherapy-induced and RT-induced diarrhea was significantly reduced in the probiotics group (pooled RRs = 0.53, 95% CI [0.39, 0.71] and 0.67, 95% CI [0.51, 0.88]).	Dosage, treatment duration, and strain of probiotic different in the studies Complex probiotic regimens versus single agent Risk of bias in the form of performance and attrition bias Definition of AE was unclear in most of the included studies Variability in patients' ages, comorbidities, tumor types, therapies received, surgery, and patient outcomes among the studies	This meta-analysis is limited by inclusion of non-RCTs. Probiotic use in patients decreased the incidence of chemotherapy and RT-induced diarrhea notably in grades 2 or 3 diarrhea. Probiotics were not found to decrease the frequency of lesser grades of chemotherapy and RT-induced diarrhea. The authors suggest there is a need for research focused on the dose–effect relationship of probiotics for chemotherapy and RT-induced diarrhea. Nurses can use this information to discuss current evidence on probiotics for patients with abdominal or pelvic cancers receiving RT, chemotherapy, and concurrent therapy. More studies need to be completed to conclude a more definitive benefit. There was unclear definition of AEs as it varied between studies, but when measured no increased incidence of AEs was noted with intervention groups compared to controls.

Reyna-Figueroa, J., Bejarano-Juvera, A.A., García-Parra, C., Barrón-Calvillo, E.E., Queipo-Garcia, G.E., & Galindo-Delgado, P. (2021). Decrease of post chemotherapy complications with the use of probiotics in children with acute lymphoblastic leukemia. *Journal of Pediatric Hematology/Oncology, 43*(4), e457–e461. https://doi.org/10.1097/MPH.0000000000001956	**Design:** Prospective cohort study. **Methods:** One group (n = 30) received *Lactobacillus rhamnosus* GG probiotic twice daily for 7 days during chemotherapy, and the other group (n = 30) received no probiotics. Caregiver-reported outcomes and data extracted from medical records were used for outcome measurement. **Sample:** 60 children (aged younger than 17 years) with acute lymphoblastic leukemia (ALL) for 30 days after chemotherapy administration The intervention group was 70% male and 30% female. The control group was 56% male and 44% female. **Setting**: Single center, Hospital Central Sur de Alta Especialidad PEMEX Picacho in Mexico City, Mexico	**Independent Variable(s):** Probiotic use with *L. rhamnosus* **Dependent Variable(s):** Temperature and symptoms, emergency department visits, number of hospitalizations, number of sepsis diagnoses, development of infection, use of antibiotics. **Intervention:** The intervention group (n = 30) received *L. rhamnosus* GG probiotic twice daily for 7 days during chemotherapy, and the control group (n = 30) received no probiotics.	Caregiver-reported outcomes Emergency department visits Number of hospitalizations Sepsis diagnosis Development of infection	**Significant:** Gastrointestinal manifestations were less prevalent in the probiotic group versus the control group (30% vs. 63%; p = 0.009), with decreases in diarrhea and nausea of greater than 60% in the probiotic group. Frequency of antimicrobial use was lower in the probiotic group (26.6% vs. 53.3%; p = 0.03) There was a greater percentage of microorganism isolation in the control group (14; 46.6%) than in the intervention group (4, 13.3%; p = 0.0000004) **Not significant: (Probiotics versus placebo)** Percentage of sepsis 6.6% vs. 23.3% (p = 0.07) Visits to the emergency department 30% vs. 33% (p = 0.07) Hospitalizations 13.3% vs 30% (p = 0.1) No complications were associated with probiotic use.	Small sample size Single blinding to intervention Reliance on caregiver reporting for symptom manifestation Lack of detailed information on caregiver measurement of symptoms Reliance on accuracy of medical records	Results were reliable and applicable to pediatric patients with ALL receiving chemotherapy. Incomplete description of data collection was a methodologic limitation. In this cohort study, pediatric patients with ALL had reductions in gastrointestinal manifestations and frequency of antimicrobial use after completing chemotherapy in combination with a maximum of 7 days of *L. rhamnosus* twice daily compared with no use of probiotics. Nurses should be aware of emerging evidence on the benefits of probiotic use. Although future research with larger sample sizes is needed, this article contributes research findings in pediatric patients that is valuable for clinical decision making.