Publikationsverzeichnis des Zentrums für erbliche Tumorerkrankungen

2020

Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database.

Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer J-P, Nakken S, Engel C, Aretz S, Jenkins MA, Sunde L, Bernstein I, Capella G, Balaguer F, Thomas H, Evans DG, Burn J, Greenblatt M, Hovig E, de Vos Tot Nederveen Cappel WH, Sijmons RH, Bertario L, Tibiletti MG, Cavestro GM, Lindblom A, Della Valle A, Lopez-Köstner F, Gluck N, Katz LH, Heinimann K, Vaccaro CA, Büttner R, Görgens H, **Holinski-Feder E, Morak M**, Holzapfel S, Hüneburg R, Knebel Doeberitz M von, Loeffler M, Rahner N, Schackert HK, **Steinke-Lange V**, Schmiegel W, Vangala D, Pylvänäinen K, Renkonen-Sinisalo L, Hopper JL, Win AK, Haile RW, Lindor NM, Gallinger S, Le Marchand L, Newcomb PA, Figueiredo JC, Thibodeau SN, Wadt K, Therkildsen C, Okkels H, Ketabi Z, Moreira L, Sánchez A, Serra-Burriel M, Pineda M, Navarro M, Blanco I, Green K, Lalloo F, Crosbie EJ, Hill J, Denton OG, Frayling IM, Rødland EA, Vasen H, Mints M, Neffa F, Esperon P, Alvarez K, Kariv R, Rosner G, Pinero TA, Gonzalez ML, Kalfayan P, Tjandra D, Winship IM, Macrae F, Möslein G, Mecklin J-P, Nielsen M, Møller P.
Genet Med. 2020;22(1):15–25.

Associations of Pathogenic Variants in MLH1, MSH2, and MSH6 With Risk of Colorectal Adenomas and Tumors and With Somatic Mutations in Patients With Lynch Syndrome.

Engel C, Ahadova A, Seppälä TT, Aretz S, Bigirwamungu-Bargeman M, Bläker H, Bucksch K, Büttner R, de Vos Tot Nederveen Cappel WT, Endris V, **Holinski-Feder E**, Holzapfel S, Hüneburg R, Jacobs MAJM, Koornstra JJ, Langers AM, Lepistö A, **Morak M**, Möslein G, Peltomäki P, Pylvänäinen K, Rahner N, Renkonen-Sinisalo L, Schulmann K, **Steinke-Lange V**, Stenzinger A, Strassburg CP, van de Meeberg PC, van Kouwen M, van Leerdam M, Vangala DB, Vecht J, Verhulst M-L, von Knebel Doeberitz M, Weitz J, Zachariae S, Loeffler M, Mecklin J-P, Kloor M, Vasen HF, German HNPCC Consortium, the Dutch Lynch Syndrome Collaborative Group, Finnish Lynch Syndrome Registry.
Gastroenterology. April 2020;158(5):1326–33.

Analysis of 3297 individuals suggests that the pathogenic germline 5'-UTR variant BRCA1 c.-107A > T is not common in south-east Germany.

Laner A, Benet-Pages A, Neitzel B, Holinski-Feder E.
Fam Cancer. 21. März 2020.

Prevalence of CNV-neutral structural genomic rearrangements in MLH1, MSH2, and PMS2 not detectable in routine NGS diagnostics.

Morak M, Steinke-Lange V, Massdorf T**, Benet-Pages A, Locher M, Laner A**, Kayser K, Aretz S, **Holinski-Feder E.**
Fam Cancer. April 2020;19(2):161–7.

2019

Targeted deep-intronic sequencing in a cohort of unexplained cases of suspected Lynch syndrome.

Arnold AM, **Morak M, Benet-Pagès A, Laner A**, Frishman D, **Holinski-Feder E**.
Eur J Hum Genet. 10. Dezember 2019;

Results of multigene panel testing in familial cancer cases without genetic cause demonstrated by single gene testing.
Dominguez-Valentin M, Nakken S, Tubeuf H, Vodak D, Ekstrøm PO, Nissen AM, **Morak M, Holinski-Feder E**, Holth A, Capella G, Davidson B, Evans DG, Martins A, Møller P, Hovig E.
Sci Rep. 6. Dezember 2019;9(1):18555.

Das Birt-Hogg-Dubé-Syndrom
Steinke-Lange V, Holinski-Feder E
TZM-News 4/2019, ISSN: 1437-8019

Survival by colon cancer stage and screening interval in Lynch syndrome: a prospective Lynch syndrome database report.
Dominguez-Valentin M, Seppälä TT, Sampson JR, Macrae F, Winship I, Evans DG, Scott RJ, Burn J, Möslein G, Bernstein I, Pylvänäinen K, Renkonen-Sinisalo L, Lepistö A, Lindblom A, Plazzer J-P, Tjandra D, Thomas H, Green K, Lalloo F, Crosbie EJ, Hill J, Capella G, Pineda M, Navarro M, Vidal JB, Rønlund K, Nielsen RT, Yilmaz M, Elvang LL, Katz L, Nielsen M, Ten Broeke SW, Nakken S, Hovig E, Sunde L, Kloor M, Knebel Doeberitz MV, Ahadova A, Lindor N, **Steinke-Lange V, Holinski-Feder E**, Mecklin J-P, Møller P.
Hered Cancer Clin Pract. 2019;17:28.

Darmkrebs: Vorsorge und Früherkennung neu geregelt
Gross M, Holinski-Feder E.
MMW Fortschr Med. 2019;161(7):43–8.

Empfehlungen zur Früherkennung, Risikoreduktion, Überwachung und Therapie bei Patienten mit Lynch-Syndrom
Hüneburg R, Aretz S, Büttner R, Daum S, Engel C, Fechner G, Habermann JK, Heling D, Hoffmann K, **Holinski-Feder E**, Kloor M, von Knebel-Döberitz M, Loeffler M, Möslein G, Perne C, Redler S, Rieß O, Schmiegel W, Seufferlein T, Siebers-Renelt U, **Steinke-Lange V**, Tecklenburg J, Vangala D, Vilz T, Weitz J, Wiedenmann B, Strassburg CP, Nattermann J.
Z Gastroenterol. November 2019;57(11):1309–20.

Full-length transcript amplification and sequencing as universal method to test mRNA integrity and biallelic expression in mismatch repair genes.
Morak M, Schaefer K, **Steinke-Lange V, Koehler U**, Keinath S, Massdorf T, Mauracher B, Rahner N, Bailey J, Kling C, Haeusser T, **Laner A, Holinski-Feder E**.
European Journal of Human Genetics. 22. Juli 2019;1.

Genetic Screening and Personalized Prevention in Colorectal Cancer.
Steinke-Lange V, Holinski-Feder E.
VIS. 2019;35(4):226–30.

The apparent genetic anticipation in PMS2-associated Lynch syndrome families is explained by birth cohort effect.
Ten Broeke SW, Rodríguez-Girondo M, Suerink M, Aretz S, Bernstein I, Capella G, Engel C, Gomez-Garcia EB, van Hest LP, von Knebel Doeberitz M, Lagerstedt-Robinson K, Letteboer TGW, Møller P, van Os TAM, Pineda M, Rahner N, Olderode-Berends MJW, von Salomé J, Schackert HK, Spruijt L, **Steinke-Lange V**, Wagner A, Tops CMJ, Nielsen M.
Cancer Epidemiol Biomarkers Prev. 1. März 2019.

Boosting care and knowledge about hereditary cancer: European Reference Network on Genetic Tumour Risk Syndromes.
Vos JR, Giepmans L, Röhl C, Geverink N, Hoogerbrugge N, **ERN GENTURIS**.
Fam Cancer. 2019;18(2):281–4.

Peutz-Jeghers-Syndrom
Steinke-Lange V, Holinski-Feder E
TZM-News 1/2019, ISSN: 1437-8019

2018

Copy number variation analysis and targeted NGS in 77 families with suspected Lynch syndrome reveals novel potential causative genes.
Kayser K, Degenhardt F, Holzapfel S, Horpaopan S, Peters S, Spier I, **Morak M**, Vangala D, Rahner N, von Knebel-Doeberitz M, Schackert HK, Engel C, Büttner R, Wijnen J, Doerks T, Bork P, Moebus S, Herms S, Fischer S, Hoffmann P, Aretz S, **Steinke-Lange V**.
Int J Cancer. 2018 Dec 1;143(11):2800-2813. doi: 10.1002/ijc.31725.

Li-Fraumeni-Syndrom
Steinke-Lange V, Holinski-Feder E
TZM-News 2/2018, ISSN: ISSN: 1437-8019

No Difference in Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies.
Engel C, Vasen HF, Seppälä T, Aretz S, Bigirwamungu-Bargeman M, de Boer SY, Bucksch K, Büttner R, Holinski-Feder E, Holzapfel S, Hüneburg R, Jacobs MAJM, Järvinen H, Kloor M, von Knebel Doeberitz M, Koornstra JJ, van Kouwen M, Langers AM, van de Meeberg PC, **Morak M**, Möslein G, Nagengast FM, Pylvänäinen K, Rahner N, Renkonen-Sinisalo L, Sanduleanu S, Schackert HK, Schmiegel W, Schulmann K, **Steinke-Lange V**, Strassburg CP, Vecht J, Verhulst M-L, de Vos Tot Nederveen Cappel W, Zachariae S, Mecklin J-P, Loeffler M, German HNPCC Consortium, the Dutch Lynch Syndrome Collaborative Group, and the Finnish Lynch Syndrome Registry.
Gastroenterology. 2018 Nov;155(5):1400-1409.e2. doi: 10.1053/j.gastro.2018.07.030.

Interdisciplinary Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer. Guideline (S3-Level, AWMF Registry Number 032/034-OL, April 2018) - Part 2 with Recommendations on the Therapy and Follow-up of Endometrial Cancer, Palliative Care, Psycho-oncological/Psychosocial Care/Rehabilitation/Patient Information and Healthcare Facilities.
Emons G, Steiner E, Vordermark D, Uleer C, Bock N, Paradies K, Ortmann O, Aretz S, Mallmann P, Kurzeder C, Hagen V, van Oorschot B, Höcht S, Feyer P, Egerer G, Friedrich M, Cremer W, Prott FJ, Horn LC, Prömpeler H, Langrehr J, Leinung S, Beckmann MW, Kimmig R, Letsch A, Reinhardt M, Alt-Epping B, Kiesel L, Menke J, Gebhardt M, **Steinke-Lange V,** Rahner N, Lichtenegger W, Zeimet A, Hanf V, Weis J, Mueller M, Henscher U, Schmutzler RK, Meindl A, Hilpert F, Panke JE, Strnad V, Niehues C, Dauelsberg T, Niehoff P, Mayr D, Grab D, Kreißl M, Witteler R, Schorsch A, Mustea A, Petru E, Hübner J, Rose AD, Wight E, Tholen R, Bauerschmitz GJ, Fleisch M, Juhasz-Boess I, Lax S, Runnebaum I, Tempfer C, Nothacker MJ, Blödt S, Follmann M, Langer T, Raatz H, Wesselmann S, Erdogan S
Geburtshilfe Frauenheilkd. 2018 Nov;78(11):1089-1109. doi: 10.1055/a-0715-2964.

Interdisciplinary Diagnosis, Therapy and Follow-up of Patients with Endometrial Cancer. Guideline (S3-Level, AWMF Registry Nummer 032/034-OL, April 2018) - Part 1 with Recommendations on the Epidemiology, Screening, Diagnosis and Hereditary Factors of Endometrial Cancer.
Emons G, Steiner E, Vordermark D, Uleer C, Bock N, Paradies K, Ortmann O, Aretz S, Mallmann P, Kurzeder C, Hagen V, van Oorschot B, Höcht S, Feyer P, Egerer G, Friedrich M, Cremer W, Prott FJ, Horn LC, Prömpeler H, Langrehr J, Leinung S, Beckmann MW, Kimmig R, Letsch A, Reinhardt M, Alt-Epping B, Kiesel L, Menke J, Gebhardt M, **Steinke-Lange V**, Rahner N, Lichtenegger W, Zeimet A, Hanf V, Weis J, Mueller M, Henscher U, Schmutzler RK, Meindl A, Hilpert F, Panke JE, Strnad V, Niehues C, Dauelsberg T, Niehoff P, Mayr D, Grab D, Kreißl M, Witteler R, Schorsch A, Mustea A, Petru E, Hübner J, Rose AD, Wight E, Tholen R, Bauerschmitz GJ, Fleisch M, Juhasz-Boess I, Sigurd L, Runnebaum I, Tempfer C, Nothacker MJ, Blödt S, Follmann M, Langer T, Raatz H, Wesselmann S, Erdogan S
Geburtshilfe Frauenheilkd. 2018 Oct;78(10):949-971. doi: 10.1055/a-0713-1218.

Cancer Risks for PMS2-Associated Lynch Syndrome.
Ten Broeke SW, van der Klift HM, Tops CMJ, Aretz S, Bernstein I, Buchanan DD, de la Chapelle A, Capella G, Clendenning M, Engel C, Gallinger S, Gomez Garcia E, Figueiredo JC, Haile R, Hampel HL, Hopper JL, Hoogerbrugge N, von Knebel Doeberitz M, Le Marchand L, Letteboer TGW, Jenkins MA, Lindblom A, Lindor NM, Mensenkamp AR, Møller P, Newcomb PA, van Os TAM, Pearlman R, Pineda M, Rahner N, Redeker EJW, Olderode-Berends MJW, Rosty C, Schackert HK, Scott R, Senter L, Spruijt L, **Steinke-Lange V**, Suerink M, Thibodeau S, Vos YJ, Wagner A, Winship I, Hes FJ, Vasen HFA, Wijnen JT, Nielsen M, Win AK.
J Clin Oncol. 2018 Oct 10;36(29):2961-2968. doi: 10.1200/JCO.2018.78.4777.

Das Cowden-Syndrom
Steinke-Lange V, **Holinski-Feder E**
TZM-News 3-4/2018, ISSN: ISSN: 1437-8019

Haplotype analysis suggest that the MLH1 c.2059C > T mutation is a Swedish founder mutation.
von Salomé J, Liu T, Keihäs M, **Morak M**, **Holinski-Feder E**, Berry IR, Moilanen JS, Baert-Desurmont S, Lindblom A, Lagerstedt-Robinson K.
Fam Cancer. 2018 Okt. doi: 10.1007/s10689-017-0067-x.

Comprehensive analysis of the *MLH1* promoter region in 480 patients with colorectal cancer and 1150 controls reveals new variants including one with a heritable constitutional *MLH1* epimutation.
Morak M, Ibisler A, Keller G, Jessen E, **Laner A**, Gonzales-Fassrainer D, **Locher M**, Massdorf T, Nissen AM, Benet-Pagès A, **Holinski-Feder** E.
J Med Genet. 2018 Feb 22. pii: jmedgenet-2017-104744. doi: 10.1136/jmedgenet-2017-104744.

Identification of genetic variants for clinical management of familial colorectal tumors.
Dominguez-Valentin M, Nakken S, Tubeuf H, Vodak D, Ekstrøm PO, Nissen AM, **Morak M**, **Holinski-Feder E**, Martins A, Møller P, Hovig E.
BMC Med Genet. 2018 Feb 20;19(1):26. doi: 10.1186/s12881-018-0533-9.

Genetic variants of prospectively demonstrated phenocopies in *BRCA1/2* kindreds.
Dominguez-Valentin M, Evans DGR, Nakken S, Tubeuf H, Vodak D, Ekstrøm PO, Nissen AM, **Morak M**, **Holinski-Feder E**, Martins A, Møller P, Hovig E.
Hered Cancer Clin Pract. 2018 Jan 15;16:4. doi: 10.1186/s13053-018-0086-0.

Role of germline aberrations affecting *CTNNA1*, *MAP3K6* and *MYD88* in gastric cancer susceptibility.
Weren RDA, van der Post RS, Vogelaar IP, van Krieken JH, Spruijt L, Lubinski J, Jakubowska A, Teodorczyk U, Aalfs CM, van Hest LP, Oliveira C, Kamping EJ, Schackert HK, Ranzani GN, Gómez García EB, Hes FJ, **Holinski-Feder E**, Genuardi M, Ausems MGEM, Sijmons RH, Wagner A, van der Kolk LE, Cats A, Bjørnevoll I, Hoogerbrugge N, Ligtenberg MJL.
J Med Genet. 2018 Jan 12. pii: jmedgenet-2017-104962. doi: 10.1136/jmedgenet-2017-104962.

Potentially pathogenic germline CHEK2 c.319+2T>A among multiple early-onset cancer families.
Dominguez-Valentin M, Nakken S, Tubeuf H, Vodak D, Ekstrøm PO, Nissen AM, **Morak M**, **Holinski-Feder E**, Martins A, Møller P, Hovig E.
Fam Cancer. 2018 Jan.

2017

Colorectal cancer incidence in *path_MLH1* carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report.
Seppälä T, Pylvänäinen K, Evans DG, Järvinen H, Renkonen-Sinisalo L, Bernstein I, **Holinski-Feder E**, Sala P, Lindblom A, Macrae F, Blanco I, Sijmons R, Jeffries J, Vasen H, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen J, Jenkins M, Genuardi M, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, **Morak M**, Frayling IM, Plazzer JP, Sampson JR, Capella G, Möslein G, Mecklin JP, Møller P; Mallorca Group.
Hered Cancer Clin Pract. 2017 Oct 10;15:18.

Unraveling genetic predisposition to familial or early onset gastric cancer using germline whole-exome sequencing.
Vogelaar IP, van der Post RS, van Krieken JHJ, Spruijt L, van Zelst-Stams WA, Kets CM, Lubinski J, Jakubowska A, Teodorczyk U, Aalfs CM, van Hest LP, Pinheiro H, Oliveira C, Jhangiani SN, Muzny DM, Gibbs RA, Lupski JR, de Ligt J, Vissers LELM, Hoischen A, Gilissen C, van de Vorst M, Goeman JJ, Schackert HK, Ranzani GN, Molinaro V, Gómez García EB, Hes FJ, **Holinski-Feder E**, Genuardi M, Ausems MGEM, Sijmons RH, Wagner A, van der Kolk LE, Bjørnevoll I, Høberg-Vetti H, van Kessel AG, Kuiper RP, Ligtenberg MJL, Hoogerbrugge N.
Eur J Hum Genet. 2017 Sep 6.

Cancer risk and survival in *path_MMR* carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database.
Møller P, Seppälä TT, Bernstein I, **Holinski-Feder E**, Sala P, Gareth Evans D, Lindblom A, Macrae F, Blanco I, Sijmons RH, Jeffries J, Vasen HFA, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen JT, Jenkins MA, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, **Morak M**, Renkonen-Sinisalo L, Valentin MD, Frayling IM, Plazzer JP, Pylvanainen K, Genuardi M, Mecklin JP, Moeslein G, Sampson JR, Capella G; Mallorca Group.
Gut. 2017 Jul 28.

Elucidating the molecular basis of msh2-deficient tumors by combined germline and somatic analysis.
Vargas-Parra GM, González-Acosta M, Thompson BA, Gómez C, Fernández A, Dámaso E, Pons T, **Morak M**, Del Valle J, Iglesias S, Velasco À, Solanes A, Sanjuan X, Padilla N, de la Cruz X, Valencia A, **Holinski-Feder E**, Brunet J, Feliubadaló L, Lázaro C, Navarro M, Pineda M, Capellá G.
Int J Cancer. 2017 Jun 2.

Loss of MSH2 and MSH6 due to heterozygous germline defects in MSH3 and MSH6.
Morak M, Käsbauer S, Kerscher M, **Laner A**, Nissen AM, Benet-Pagès A, Schackert HK, Keller G, Massdorf T, **Holinski-Feder E**.
Fam Cancer. 2017 May 20.

Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database.
Møller P, Seppälä T, Bernstein I, **Holinski-Feder E**, Sala P, Evans DG, Lindblom A, Macrae F, Blanco I, Sijmons R, Jeffries J, Vasen H, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen J, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, **Morak M**, Renkonen-Sinisalo L, Frayling IM, Plazzer JP, Pylvanainen K, Sampson JR, Capella G, Mecklin JP, Möslein G; Mallorca Group (http://mallorca-group.eu).
Gut. 2017 Mar;66(3):464-472.

2016

Identification and Functional Testing of ERCC2 Mutations in a Multi-national Cohort of Patients with Familial Breast- and Ovarian Cancer.
Rump A, Benet-Pages A, Schubert S, Kuhlmann JD, Janavičius R, Macháčková E, Foretová L, Kleibl Z, Lhota F, Zemankova P, Betcheva-Krajcir E, Mackenroth L, Hackmann K, Lehmann J, Nissen A, DiDonato N, Opitz R, Thiele H, Kast K, Wimberger P, **Holinski-Feder E**, Emmert S, Schröck E, Klink B.
PLoS Genet. 2016 Aug 9;12(8):e1006248.

Exome Sequencing Identifies Biallelic MSH3 Germline Mutations as a Recessive Subtype of Colorectal Adenomatous Polyposis.
Adam R, Spier I, Zhao B, Kloth M, Marquez J, Hinrichsen I, Kirfel J, Tafazzoli A, Horpaopan S, Uhlhaas S, Stienen D, Friedrichs N, Altmüller J, **Laner A**, Holzapfel S, Peters S, Kayser K, Thiele H, **Holinski-Feder E**, Marra G, Kristiansen G, Nöthen MM, Büttner R, Möslein G, Betz RC, Brieger A, Lifton RP, Aretz S.
Am J Hum Genet. 2016 Aug 4;99(2):337-51.

Incidence of and survival after subsequent cancers in carriers of pathogenic MMR variants with previous cancer: a report from the prospective Lynch syndrome database.
Møller P, Seppälä T, Bernstein I, **Holinski-Feder E**, Sala P, Evans DG, Lindblom A, Macrae F, Blanco I, Sijmons R, Jeffries J, Vasen H, Burn J, Nakken S, Hovig E, Rødland EA, Tharmaratnam K, de Vos Tot Nederveen Cappel WH, Hill J, Wijnen J, Jenkins M, Green K, Lalloo F, Sunde L, Mints M, Bertario L, Pineda M, Navarro M, **Morak M**, Renkonen-Sinisalo L, Frayling IM, Plazzer JP, Pylvanainen K, Genuardi M, Mecklin JP, Möslein G, Sampson JR, Capella G; Mallorca Group (http://mallorca-group.org).
Gut. 2016 Jun 3. pii: gutjnl-2016-311403.

Exome sequencing identifies potential novel candidate genes in patients with unexplained colorectal adenomatous polyposis.
Spier I, Kerick M, Drichel D, Horpaopan S, Altmüller J, **Laner A**, Holzapfel S, Peters S, Adam R, Zhao B, Becker T, Lifton RP, **Holinski-Feder E**, Perner S, Thiele H, Nöthen MM, Hoffmann P, Timmermann B, Schweiger MR, Aretz S.
Fam Cancer. 2016 Apr;15(2):281-8.

Low-level APC mutational mosaicism is the underlying cause in a substantial fraction of unexplained colorectal adenomatous polyposis cases.

Spier I, Drichel D, Kerick M, Kirfel J, Horpaopan S, **Laner A**, Holzapfel S, Peters S, Adam R, Zhao B, Becker T, Lifton RP, Perner S, Hoffmann P, Kristiansen G, Timmermann B, Nöthen MM, **Holinski-Feder E**, Schweiger MR, Aretz S.

J Med Genet. 2016 Mar;53(3):172-9.